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ARTERIAL EMBOLISM AND THROMBOSIS IN INFANCY

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Arterial thrombosis and arterial embolism are l recognized entities in adult patients and e received extensive consideration in medical rnals and textbooks. Little attention has, vever, been paid to such vascular occlusions young subjects, particularly infants.

Dohan [1] made an excellent review of the literae on gangrene of the extremities in the newn, and much of the information included in accompanying table was compiled from the a which he gathered. Heller and Alvari [2] wise presented an admirable review of gane of the extremities in newly born babies. rtin and Shore [3] studied 4 patients, ranging in from 4 to 14 years, with gangrene of the exmities. These writers particularly emphasized role of severe sepsis in production of arterial ombosis in children. Their discussion cened principally on lesions of older subjects and l little to do with infants. Von Khautz [4] lected a group of 50 cases of gangrene in ients varying in age from newborn infants to ldren of 15 years. Besides 34 infants, the ct ages of whom were not given, there were children of various ages up to 15 years. Von autz supplied an extensive bibliography, which f great value to any one interested in gangrene the extremities in older children.

PERSONAL OBSERVATIONS

Though my material is limited, it indicates that rtial or complete obstructions can appear in ge arteries in almost any part of the body. ave found them in the hand and arm (axillary tery), the leg (iliac arteries or lower part of the aorta), the foot (plantar artery), the spleen, the kidney, the brain and the lung.

Arterial obstruction is most easily recognized when it occurs in the arm or leg, where the effects of ischemia are readily apparent. Given an extremity which was previously normal, the sudden onset of coldness or pallor, diminution or loss of muscular power, discoloration of the skin or lack of pulsation in the vessel supplying the part, all give obvious and indisputable evidence of an acute vascular accident. At first it may be difficult to differentiate between spasm of the regional artery and actual blockage of its lumen. If the affected vessel is a large one, such as the axillary or the external iliac artery, spasm (sufficient to cause ischemia) would be most unlikely. Furthermore, the persistence of a diminished blood flow for more than an hour or two would certainly be more indicative of arterial occlusion than of spasm.

After an ischemic insult, the tissue changes may be either severe and productive of gangrene or mild and reversible. The extent and grade of the damage depend on the size of the vessel which is obstructed and on the ability of the collateral circulation to redistribute the blood in a satisfactory manner. Pallor of the skin is almost invariably followed in a few hours by a bluish and mottled discoloration, of variable degree. If gangrene is to supervene, a line of demarcation will almost certainly appear within twenty-four to forty-eight hours; this dividing line will sharply indicate which part of the extremity will survive and which portion will ultimately die. However, if the arterial occlusion is incomplete, or if the collateral circulation is sufficient to carry the load, the pallor or cyanosis will gradually disappear and will be progressively replaced by a more pinkish tint. This improvement may be slow and may not be pronounced for a week or more. With the gradual return of the color toward a normal state, the temperature of the part will progressively rise, even though it may not approximate normal for many weeks, or indeed for several months. Circulatory impairment is not limited to the skin and sub-

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1. Dohan, F. C.: Gangrene of an Extremity in a wborn Infant, with Review of the Literature, J. diat. **5**:756, 1934.
2. Heller, G., and Alvari, G.: Gangrene of the tremities in the Newborn: Occurrence of Functional covery, Am. J. Dis. Child. **62**:133 (July) 1941.
3. Martin, W., and Shore, B. R.: Juvenile Gangrene, n. Surg. **88**:725, 1928.
4. von Khautz, A.: Spontane Extremitätengangrän Kindesalter, Ztschr. f. Kinderh. **11**:35, 1914.

cutaneous tissues; it likewise involves the underlying muscles. Loss of motor power does not necessarily indicate irreparable damage, because paralysis can be followed by return of muscular function, even though many months may be required for reestablishment of full strength. If the ischemia has been severe, fibrosis and resulting shortening of muscle bellies may lead to deformities, particularly those of the flexion-contraction type. While paralysis or muscle cicatrization can be alarming at first, it is well to point out that total recovery or functional rehabilitation of the limb is still possible.

Unless the changes are striking, it is usually impossible to make an early and accurate prediction regarding the ultimate survival or necrosis of an involved extremity. The evidence of vascular impairment may be great, and yet eventual recovery may be complete. Certainly, I have gained the distinct impression that the collateral circulations of an infant are more adaptable and can assume greater burdens than would be the case with similar major arterial obstructions in adults.

Blockage of a renal artery may be suspected from an elevation of the blood urea nitrogen or from the passage of albumin, blood or casts in the urine. If renal impairment is bilateral, oliguria or anuria may follow. Such changes in the blood chemistry, the urinary constituents or the fluid output are commonly produced by other conditions, such as nephritis or ureteral blockage, but if they appear in the presence of infarction elsewhere in the body, particularly in the legs, one is justified in suspecting that the renal pathologic change is likewise on the basis of an obstruction in the renal arteries.

Damage to the brain by arterial occlusion may produce a clinical picture which is either readily recognizable or extremely confusing. Neurologic changes, including paralyses, flaccidity or hypertonicity, nystagmus, convulsions and loss of consciousness, can appear suddenly or have an insidious onset. The symptoms and signs can be focal and thus indicate the area of damage to the brain; in contrast, the picture may be so bizarre that it is impossible to determine what part of the central nervous system is affected. If neurologic symptoms appear in an infant without evidence of disease elsewhere in the body, one is likely to suspect meningitis, birth injury or intracranial bleeding on the basis of a hemorrhagic diathesis rather than intracranial arterial thrombosis. If, however, there is concomitant evidence of arterial obstruction in some other part of the body, it is reasonable to assume that the damage to the brain is secondary to intracranial arterial thrombosis or embolism.

Arterial occlusions often occur in the absence of demonstrable cardiac disorder. Indeed, in the present series they were more common when there was no clinical evidence of cardiac abnormality (5 cases) than when cardiac malformation was known to exist (1 case).

REPORT OF CASES

CASE 1.—A. A. was born Dec. 2, 1941 by cesarean section and was attended by Dr. Joseph Merriam, Framingham, Mass. At the time of birth and shortly thereafter the baby was thought to be entirely normal. Within three or four hours a lesion of the left foot was noticed. When the child was seen in consultation at about 8 hours of age, he was active and was healthy in appearance; there was no cardiac murmur. Pathologic findings were limited to the left foot, the outer three toes of which were bluish and cold. The discoloration extended from onto the dorsum and the sole of the foot for about 1 cm. beyond the base of the toes and about 3 cm. along the

Fig. 1 (case 1).—*A*, photograph of the foot at 2 months of age, showing loss of substance (by spontaneous amputation) of three lateral toes. *B*, roentgenogram of the foot at the same age, indicating loss of bony structure, after gangrene and spontaneous amputation.

lateral border of the foot. The skin was unbroken and was not blistered. A careful review of the events during and after delivery made us feel certain that there had been no mechanical or thermal injury to the foot. The foot was normally formed, and all of the changes appeared to represent arterial occlusion of terminal vessels within the foot itself. Pulsation of the dorsalis pedis artery could be felt. It was the impression at the time that the arterial supply was probably occluded in the tarsal and arcuate branches of the dorsalis pedis artery; possibly the lateral plantar division of the posterior tibial artery was blocked. Because the changes were so striking, there appeared to be little doubt that the regional skin, if not the deeper structures, would subsequently slough away. Because of this, every effort was made to keep the foot as clean as possible; it was carefully washed with alcohol and was kept in a sterile dressing, which was changed daily. By the fourth or fifth day, all of the discolored skin was dark, and the

had become swollen and blistered. The gangrene me deeper, and by the end of the first week the and subcutaneous tissues completely sloughed away, ly exposing the underlying tendons and bones. ing the third week, spontaneous amputation occurred, hat the distal phalanx of the middle toe, half of the th toe and all of the fifth toe dropped off. Fortu-ly, there was no superimposed infection. The cuta-us margins of the wound proliferated, so that skin w in from the edges and completely covered the nulating surface by the end of the fourth week of life. ince the time of final closure of the wound there e been no complaints referable to the limb except the cosmetic appearance of the foot. The child has d and walked in a satisfactory manner. When he last examined, at 27 months of age (fig. 1 *A* and *B*), remainder of the foot was warm and of normal or. The skin over the healed area was of sufficient kness and durability to withstand the pressure of ght bearing.

he child has never shown any evidence of arterial lusion in other extremities or in any other organ.

ASE 2.—R. R., a boy, was delivered by Dr. Saul man, on Sept. 4, 1942. The birth was normal. re was no known trauma to the right arm; the d was not wrapped around the arm, nor had this remity prolapsed alongside the oncoming head. A hours after delivery it was noted that the right d and the entire right forearm were distinctly cold very pale. Shortly after this the parts became in-ely blue and mottled; there was an obvious, severe ulatory impairment. The child was seen in consul-on at this time, and the following observations were de:

he baby was well developed and vigorous and showed variation from the normal except for the right arm. e heart was normal in size; there were no murmurs. e circulation was adequate in each leg and in the left n. The right hand and forearm were cyanotic and d as compared with the left arm. There was no sation in the radial artery, the brachial artery or axillary artery on the right, though pulsations in the responding arteries on the left could be readily felt. e muscular power was greatly impaired, and there re but feeble movements of the fingers and wrist on right, even when the baby was sharply stimulated. e findings suggested an occlusion of the axillary ery or of some portion of the right subclavian artery. he entire right arm was cleansed with alcohol and pt in a sterile dressing, to diminish the danger of osis in case subsequent sloughing should occur. The essings were changed daily and were maintained for o weeks. During the first four or five days, the nounced bluish discoloration continued, and swelling the hand and forearm appeared. The limb was com-tely flaccid from the elbow downward, and its general tus was such that impending gangrene and the neces-y of an amputation were strongly considered. On e sixth or seventh day the bluish discoloration was a le less pronounced, and it became progressively less tense during the following week. Concurrently, some nk color began to appear, becoming gradually more ominent. During the second week the swelling of e hand and forearm slowly subsided and finally dis-peared. By the end of the second week the general lor had improved to a degree which made me feel rtain that the circulation would be adequate for main-ining life in the limb; however, there was as yet no idence of muscular power, nor was there any detect-le pulsation in any part of the right arm. Toward e end of the third week the extremity had a rather nk color but was still a little mottled; movements were now beginning to appear in the fingers and at the wrist, though these were extremely weak. At 2½ months of age considerable improvement was evident, since active extension and flexion of the fingers and wrist were fairly good; but it was obvious that some shortening was taking place in the flexor muscles of the fingers. The fingers could not be passively stretched out into complete extension; the shortening of the flexor muscles was presumably dependent on the previous ischemia and subsequent scar formation. In an effort to overcome this deformity, the mother was instructed to massage the forearm and frequently to stretch the fingers.

When the child was 6 months of age, the fingers could be completely extended, and there was good muscular power in all of the fingers and in the wrist. No pulsation could yet be detected in the right radial, brachial or axillary arteries, though the limb was warm and its color was normal.

At the age of 17 months a faint pulsation could be felt in the right radial artery for the first time. This pulsation gradually increased in intensity during subsequent observations.

When the child was last seen, at the age of 26 months (fig. 2), the hand and forearm were entirely normal in size, color, warmth, development and muscular power. Pulsations in the radial, brachial and axillary arteries on the right side were as intense as those in the corresponding vessels on the left.

Fig. 2 (case 2).—Photograph of the hand and forearm at 26 months of age, showing normal appearance, though there had been impending gangrene in the first week of life.

CASE 3.—E. A. K., an 8 day old baby, entered the hospital Nov. 7, 1942. There had been an uneventful pregnancy and a normal delivery. A slight equinovarus deformity on the left foot and ankle was noted, but no other disturbance was observed during the first few days of life. On the seventh day a large portion of the left leg suddenly became blue, with a sharp line of demarcation in the lower third of the thigh. From that time, thirty-four hours before hospitalization, the lower two thirds of the leg continued to be bluish and mottled. Some hours after these changes were first noted in the leg, a throat stick splint was applied to the outer surface of the lower leg in such a way as to support the foot. Because of impaired circulation in the extremity, this splint was removed by the attending physician within twenty minutes. (Whether application of the splint had anything to do with the subsequently described cutaneous necrosis is open to question. Certainly, it had no bearing on the extensive vascular disturbances in the leg, but it could have precipitated the destruction of skin along the side of the leg, in an extremity with an already impaired blood supply.)

The baby cried vigorously, was alert and seemed essentially normal except for the changes in the left leg. The heart appeared normal; no murmur was heard. The muscular power of the left leg was diminished, and the limb was flaccid. There was a mild equinovarus deformity of the left foot. The entire left lower leg seemed cold when compared with the right one. There was a slight, purplish, irregular discoloration of the entire lower leg and foot. This change was especially intense over the lateral aspect where there were cutaneous blebs, indicating impending gangrene. When the child lay in bed, the discoloration extended

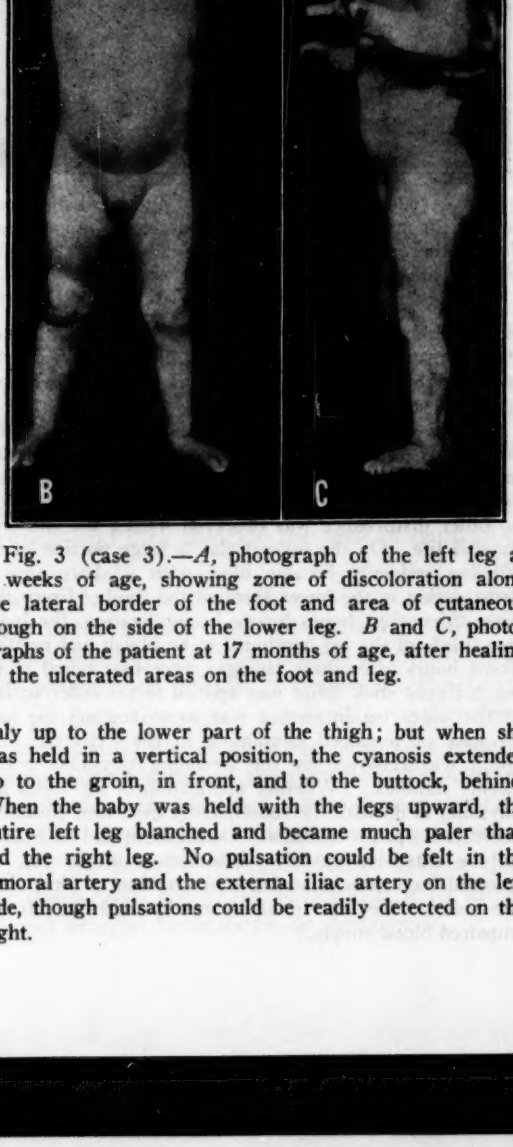

Fig. 3 (case 3).—*A*, photograph of the left leg at 2 weeks of age, showing zone of discoloration along the lateral border of the foot and area of cutaneous slough on the side of the lower leg. *B* and *C*, photographs of the patient at 17 months of age, after healing of the ulcerated areas on the foot and leg.

only up to the lower part of the thigh; but when she was held in a vertical position, the cyanosis extended up to the groin, in front, and to the buttock, behind. When the baby was held with the legs upward, the entire left leg blanched and became much paler than did the right leg. No pulsation could be felt in the femoral artery and the external iliac artery on the left side, though pulsations could be readily detected on the right.

Repeated urinalyses all gave normal findings. The red cell counts varied from 5,300,000 to 3,400,000, the white cell counts, from 18,800 to 9,600 cells, cubic millimeter. A Wassermann reaction of the bl was negative.

Immediately after hospitalization of the child, lumbar sympathetic nerves on the left side were bloc by injection of 5 cc. of 1 per cent solution of proc hydrochloride. This infiltration was repeated on e of three succeeding days. After each of these infil tions the circulation in the left leg appeared slig improved. For the first forty-eight hours of patient's hospitalization the extremity was kept i dry sterile dressing and encased in an ice pack, in or to reduce its oxygen consumption. For four days leg was alternately elevated and lowered, in the h of enhancing its circulation. Approximately one w after the patient's admission it was evident that a l area on the outer side of the lower leg would slo (fig. 3 *A*). This zone was treated with diluted solu of sodium hypochlorite and with liquid petrola dressings, which were changed daily. A clean, gra lating area developed over the side of the leg a another over the lateral aspect of the heel; these ar gradually became smaller by the ingrowth of skin f their margins. By the end of two months these r areas had been completely covered by scar tissue a new skin. During this time the circulation in the en leg had gradually improved. All cyanosis disappea While the general muscular tone of the extremity i proved, a rather pronounced degree of foot drop p sisted. After complete cutaneous healing had b obtained, a plaster cast boot was applied for treatm of the talipes deformity and for support to the foot u such time as the muscular power in the extensor mus should return. The child was discharged from the h pital on Jan. 11, 1943; at this time there was perceptible pulsation in the left femoral or the exte iliac artery.

The girl was followed in the outpatient departm until November 1944. During the first three months this time plaster cast splints were employed for corr tion of the deformity of the left foot. Massage of foot and leg was then employed for about six mont At all times there was fairly good circulation in t leg as far as could be determined by its color and te perature. There was no pulsation of the femoral art until the child reached 16 months of age, when a faint definite beat could be felt. The left limb has not develo so well as the right one. There is still, at the time writing, some atrophy of the muscles of the thigh a noticeable disparity in size between the muscles of t lower left leg and those of the right leg. Delay growth of the left leg has become increasingly appare so that now, at the age of 24 months, the left leg ¾ inch (1.8 cm.) shorter than the right, according both external measurements and teleoroentgenogra (fig. 3 *B* and *C*). The child walks with considera facility but has an obvious limp because of the und development of the muscles of the left leg and t shortness of the limb. Good pulsations can be felt the left femoral and external iliac arteries; these pul tions are quite as forceful as those in the correspond vessels on the right side.

Case 4.—B. B. G., a 3 day old boy, entered the h pital on Aug. 13, 1943, with the chief complaint vomiting and fever, of two days' duration. His deliv was normal, and nothing unusual was noted in t following twenty-four hours.

Physical examination at the time of his hospitalizati revealed injection of both ear drums and obliterati

the landmarks. The temperature was 102 F. The gs were clear. The heart was not enlarged. The nds were of good quality; no murmur was heard. It s the impression on his admission that the child was fering from acute otitis media.

Because of unexplained lethargy, the child was kept the hospital for further observation. On the seventh it was noted for the first time that the right leg a dark bluish discoloration from the knee downward. en the leg was raised above the horizontal for eral minutes, it blanched and was waxy and pale appearance. No pulsations could be felt in the oral or the external iliac artery, though pulsations ld be felt fairly well in the corresponding arteries the left side. Reexamination of the heart showed murmur. During the course of the following two eks, the appearance of the right leg gradually re- ned to normal, and the coldness of the foot and the almost entirely disappeared. By the end of two eks there was scarcely any demonstrable difference

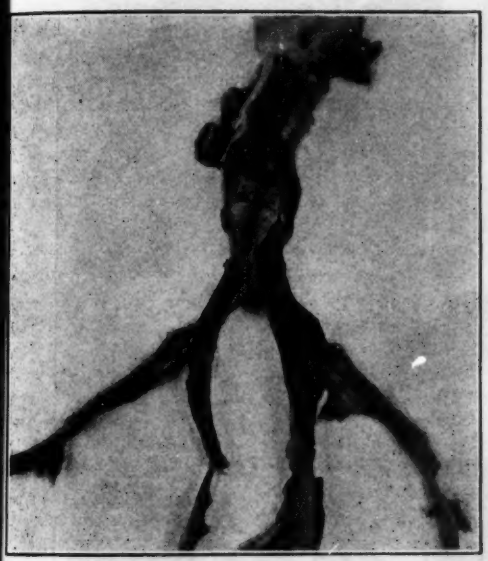

Fig. 4 (case 4).—Photograph of the lower part of the rta and the pelvic arteries, showing thrombus (which parently originated in the hypogastric arteries) ex- nding from the internal iliac arteries through the mmon iliac vessels up into the lower part of the aorta.

tween the two legs. At this time good pulsation uld be felt in both femoral arteries.

On the fourteenth day in the hospital the child sud- nly became cyanotic and had great difficulty in eathing. Concurrently with this condition persistent arrhea developed. Simultaneously, the urine contained large trace of albumin, a few casts and 15 white ood cells per high power field. The findings on roent- nographic examination of the chest were interpreted indicating patchy, bilateral bronchopneumonia. The ness ran a progressively downhill course; the child came weaker and began to have generalized edema. ne day before his death there was a sudden circulatory sturbance in both lower legs, which were very cold. a horizontal position the legs were extremely cya- tic, but on elevation they became very pale. At this ne no pulsation could be felt in either femoral artery. eath occurred on the patient's sixteenth day in the spital.

On postmortem examination[5] there was no evidence intracranial disease. From the heart's blood the colon bacillus and the beta hemolytic streptococcus were cultured (presumably representing only a terminal infection). There was no evidence of pathologic change within the heart itself. The ductus arteriosus was almost entirely closed off on its pulmonary end but was patent throughout its length and contained a firm clot. On histologic examination this thrombus was found to be of recent origin and free from any evidence of organization. In the lowest 3 cm. of the aorta was a large thrombus, which extended down into the common iliac artery and into the hypogastric artery on each side. The upper end of this extensive thrombus was just below the origin of the renal vessels. While these clots were large (fig. 4) and in some places the thrombi were intimately attached to the underlying walls, they did not entirely obstruct the lumen of the various vessels. Sections of the thrombus were made at various levels in order to study the extent of organization in its different parts. The upper and lower ends showed some beginning organization by ingrowth of connective tissue, whereas the central part of the mass showed rather extensive connective tissue organization, of a much older degree. Certainly, the clot had been of much longer standing than anything which was found in the ductus arteriosus. While it is of course conceivable that a small thrombus previously became dislodged from the ductus into the lower abdominal vessels and progressed to organization in that position, it was the distinct impression that the degenerative changes were most prŏnounced in the hypogastric arteries and that extension of the thrombosis had taken place from these vessels.

CASE 5.—P. D., a 2 week old girl, entered the hospital June 30, 1933, because of cyanosis and labored respiration, of one day's duration. The baby was delivered with high forceps, after a twenty-nine hour labor. No abnormalities were noted at birth or immediately thereafter. The child was in good physical condition until the day before her hospitalization. For twenty-four hours the parents noticed that the patient had recurring cyanosis, which varied somewhat in intensity from time to time but did not completely disappear during any portion of this period. The respirations became gradually more labored. The baby vomited once.

The infant was fairly well developed and nourished; she was acutely ill, lethargic and almost comatose. The breathing was rapid and irregular. There was cyanosis of moderate degree. The anterior fontanel was more tense than normal. The pupils were irregular but reacted to light. The heart sounds were of poor quality; no murmur was heard. The liver was considerably enlarged, and its edge could be felt 2.5 cm. below the costal margin. The extremities were normal. The knee jerks were elicited with difficulty.

During the course of the infant's hospitalization, two blood counts showed white cell levels of 31,100 and 22,700 and red cells counts of 3,140,000 and 3,990,000 per cubic millimeter. A culture of the blood yielded no pathogens. On the patient's admission the urine was entirely normal, but three days later it contained a large trace of albumin. A roentgenogram of the chest showed moderate enlargement of the heart, the transverse diameter being 6.3 cm., while the internal diameter of the chest was 11.3 cm. There was slight mottled congestion of each lung field.

With use of an oxygen tent, the cyanosis was greatly but not completely relieved. On the day after her entry the baby became alert and responsive. The heart sounds

5. Dr. Sidney Farber and his assistants made the pathologic observations in this and in the succeeding cases.

remained of poor quality; again, no murmur was heard. Daily temperatures ranged from 100 to 100.4 F. It was the impression of the staff that the patient had congenital heart disease of an undetermined type and superimposed bronchopneumonia. Toward the end of a week to be well on the road to recovery when, without premonitory signs, she was found dead in bed, on morning of the ninth day in the hospital. At no during her hospitalization was any change noted in legs which pointed to occlusive vascular disease.

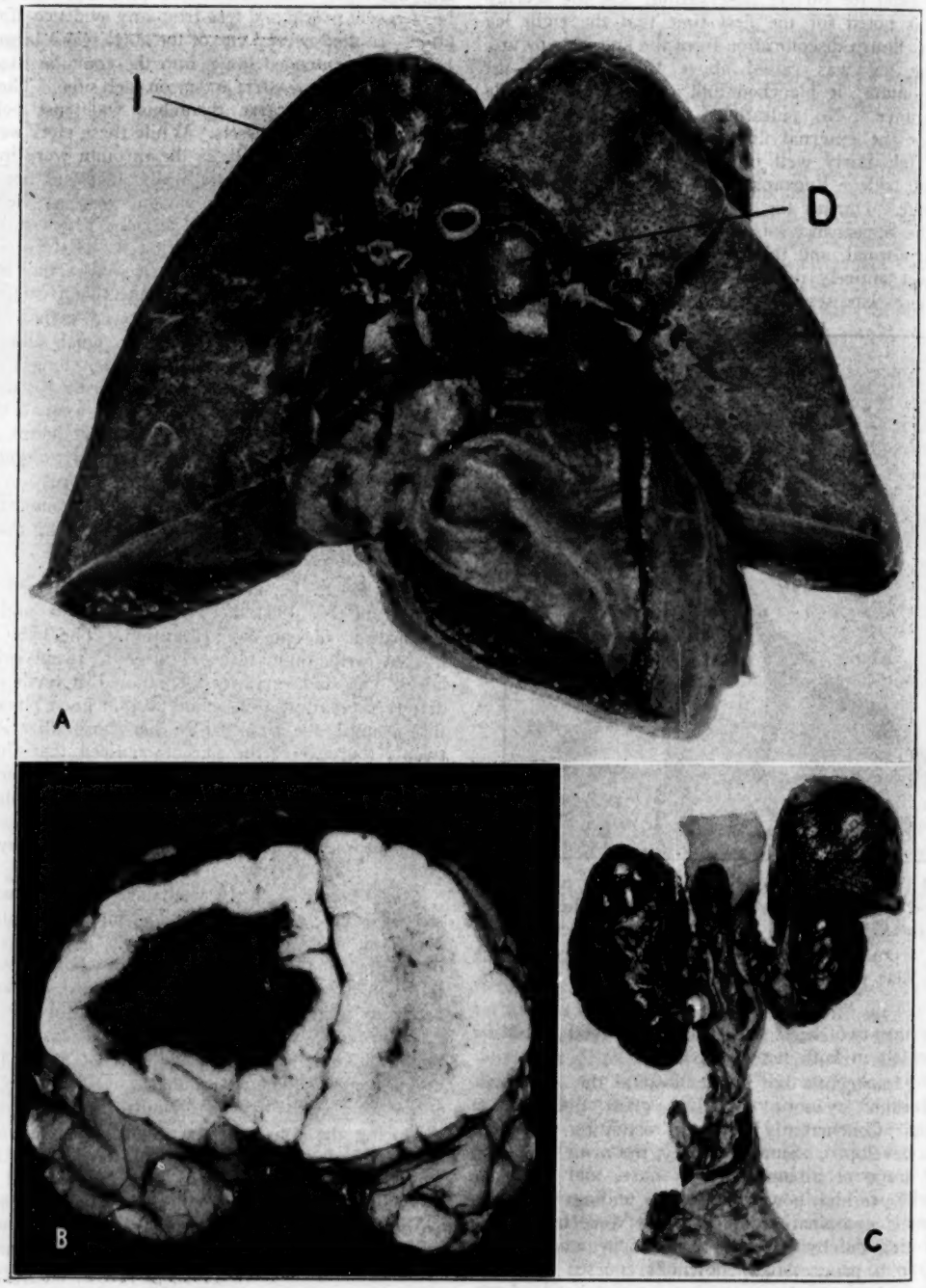

Fig. 5 (case 5).—*A*, photograph of the organs of the chest, showing distended ductus arteriosus (*D*), which w filled with a large blood clot, and infarct (*I*) of the upper lobe of the right lung. *B*, photograph of the bra indicating extensive area of infarction in the right frontal lobe. *C*, kidneys, right adrenal and abdominal aor (opened from behind), showing organizing thrombus in aorta, which extends down into the left common il artery, infarction and hemorrhage of the right adrenal and congenital hypoplasia of the right kidney.

the child's general condition had gradually improved to a point at which she could be kept out of the oxygen tent for the major portion of the day. She was thought

On postmortem examination the outstanding findi was extraordinary dilatation of the ductus arterios and thrombosis of this vessel. The ductus was 1 c

ength and 1.1 cm. in maximum diameter (fig. 5 A). thrombus which it contained was lightly attached its wall. Apparently arising from the point of chment, emboli had been thrown off into both the nonary and the peripheral arterial circulation. In upper lobe of the right lung there was a large in-t, involving more than one half of the lobe. The nch of the pulmonary artery leading to this area was d with a firmly adherent, organizing thrombus, ch almost entirely occluded its lumen. A large ion of the brain was extensively destroyed as a lt of hemorrhagic infarction (fig. 5 *B*). A necrotic , 3 by 4 by 5 cm., in the central part of the frontal extended backward to involve the basal ganglions. thin the abdominal aorta there was a laminated, mortem thrombus, extending downward into the ic arteries (fig. 5 *C*). There seemed little doubt the thrombus had originated as an embolus from ductus arteriosus. The aorta and the pelvic vessels e largely but not completely occluded by the clot. thrombus extended into both renal arteries. The t kidney showed congenital hypoplasia but, in addi-, was infarcted. The left kidney was hyperplastic. re were massive hemorrhage and softening of the t adrenal gland.

ASE 6.—J. L., a 13 month old boy, entered the hos-l Jan. 13, 1944, with a chief complaint of right iplegia, of twenty-four hours' duration. The baby's h had been normal, but immediately thereafter nosis of severe degree was noted. During the first r of life the child had been frequently studied in cardiac clinic because of intermittent spells of nosis of varying degree. The heart was known to slightly enlarged. There had always been a promi-t systolic murmur. Consultants expressed the opinion the cardiac malformation probably represented a alogy of Fallot. In spite of an obviously severe urbance in cardiac function, the general develop-nt of the child had been fairly satisfactory; at 10 nths of age he weighed 17 pounds 9 ounces (8,066 .).

The present illness began about three weeks before hospitalization. It was ushered in by occasional ts of vomiting, which increased in frequency and erity, so that eventually most of the feedings were cted. For one week the child had been unable to in anything except ice cream, ginger ale and orange e. During this time, progressive muscular weak-s was noted, and there was an increasing tendency fall toward the right. For several days the child le little effort to stand or walk. On the day before admission a deep stupor appeared, and about twelve rs later there was complete paralysis of the right n and leg.

Physical examination revealed that the baby was thin, tinctly cyanotic and in a semicomatose state. Occa-nally he could be roused, and he was then irritable l fretful. There was a rough, rather loud systolic rmur over the entire precordium. The nails of the gers and toes were prominently clubbed. There was siderable flaccidity of the muscles of the right side the body and of the right arm and leg. Most of time there was no movement of the right arm and , in contrast to normal motor activity on the left e. However, this paralysis was incomplete, because right extremities were moved when the child was ficiently stimulated. Sensation over the right side of body appeared subnormal. The neck was slightly ff. Reflexes in the extremities were essentially the e on the two sides except for the Babinski reflex, ich was definitely positive on the left side and ques-nably present on the right.

The urine was normal. Seven blood counts made during the child's hospitalization showed white cells varying from 15,100 to 6,200 per cubic millimeter. The red cell count was 7,460,000 cells per cubic millimeter on the patient's admission, rising to 8,480,000 the following day and never falling below 7,190,000 at any time. The Hinton test for syphilis gave a negative reaction. Examination of the spinal fluid at the time of the patient's admission showed normal pressure and dynamics, a total protein of 13.3 mg. per hundred cubic centimeters, no red blood cells and 5 white blood cells (all polymorphonuclear leukocytes) per cubic millimeter.

Subdural taps over the left cerebral cortex produced 2 cc. of xanthochromic fluid; from the right side about 10 cc. of similar fluid was obtained. On subsequent tapping larger amounts of fluid, up to 15 cc., were withdrawn from the subdural space on each side of the head.

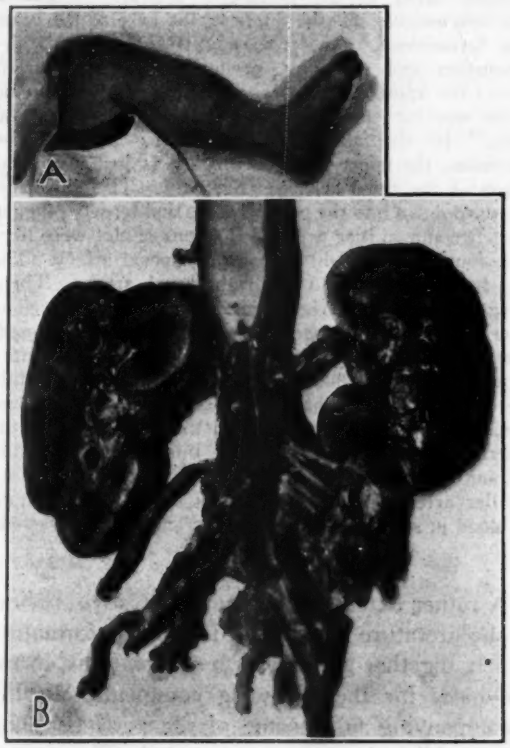

Fig. 6 (case 6).—*A*, photograph of the left leg at the time of impending gangrene of the foot and lower portion of the leg. *B*, necropsy specimen, showing embolus in the lower part of the aorta (blocking the renal vessels and extending into the common iliac arteries).

On the patient's eighteenth day in the hospital a small ecchymotic area, about 2 cm. in diameter, was first noted on the surface of the left heel. Within the next twenty-four hours this reddish discoloration spread so as to involve all of the foot and the inferior half of the lower leg. Palpation of the arterial system revealed no pulsation in the femoral or the external iliac artery on the left side; good pulsation could be felt on the right. Three days later the circulation in the right leg was obviously becoming impaired, because there were now pallor and considerable coldness of the foot and leg below the knee. Palpation showed no evidence of pulsation in the right femoral and external iliac arteries. Simultaneously, the left lower leg and foot became progressively bluer and colder. During the last two

days of life the signs of circulatory impairment progressively increased in both legs. The right foot and lower portion of the extremity became extremely cold and blanched in appearance, while the left foot and lower leg became much darker and obviously were gangrenous (fig. 6*A*). Because of the extremely poor condition of the patient, resulting from a serious cardiac disorder and an extensive cerebral injury, no therapeutic measures to improve the circulation of the legs were attempted. The baby's temperature gradually rose, reaching a maximum of 103 F. just before his death, on the twenty-third day in the hospital.

Postmortem examination showed a congenital cardiac malformation with a tetralogy of Fallot. The ductus arteriosus was open and contained on its aortic end a pinkish, firm thrombus, which protruded for several millimeters into the lumen of the aorta. Apparently arising from this site, emboli had been given off into multiple areas in the peripheral arterial circulation. The left internal carotid artery at the base of the brain was thrombosed. There were extensive cerebral degeneration and softening, predominantly on the left side of the brain. Thrombi, of recent origin, were found in the superior longitudinal sinus and within the cerebral veins. In the abdominal aorta was an extensive thrombus, the upper limit of which was just above the origin of the renal arteries (fig. 6*B*). This thrombus extended down into the pelvic vessels and largely plugged the left common iliac artery. Portions of clot were likewise found in the right superficial femoral artery. The clot had extended into the right renal artery. There were infarcts of the right kidney and the spleen. The inferior mesenteric artery was partially thrombosed. The gangrenous degeneration of the left lower extremity showed no changes due to superimposed infection. While there seemed little doubt that the various arterial obstructions had started as emboli from the clot in the ductus arteriosus, the polycythemia of this patient probably accounted for the propagation of these thrombi into smaller arteries and also probably induced the clotting of blood in some parts of the intracranial venous system.

ETIOLOGIC FACTORS

A rather extensive, but not exhaustive, review of the literature has afforded certain information which, together with my own observations, forms the basis for the following comments. In the accompanying table some of the pertinent data from published cases are presented. There were other reports prior to 1900, but many of them were brief; a few of the early records have been summarized because of their historical interest. All pertinent cases which could be found reported from 1900 to the present time—a total of 37 cases, which includes my own 6 cases—are included in the table.

In the material which has been gathered for study, infarction or gangrene involved a lower extremity in 28 cases, the upper extremity in 13 cases, the lung in 4 cases, the kidneys in 4 cases, the brain in 2 cases, the scalp in 1 case, mesenteric vessels in 3 cases and miscellaneous areas in 4 cases.

It is important to observe the ages of the patients, since it is evident that the vast majority of the arterial obstructions appear within the first two or three weeks of life and are not distribu with equal frequency throughout the years childhood. This overwhelming preponderance arterial vascular accidents within the neona period certainly suggests that most of them ha some relationship to the circulatory readjustme which normally occur after birth.

An important aspect of the study of arter occlusions in early life must necessarily be t etiology of these conditions. When one is su marizing the material which is available in t literature, it is extremely disappointing to fi that only meager evidence is available on th point. Whenever spontaneous recovery has tak place, there is of course little chance to off sound conclusions regarding the etiologic facto When an infant has died after extensive gangre autopsy is often not done, or postmortem chang are poorly described. In many instances occl sion of a major artery has been observed, b only theoretic reasons are listed for the produ tion of this blockage. Such factors are frequen recorded as "thromboangiitis obliterans," "bir trauma," "injury from an encircling umbilic cord," etc. The vast majority of these impressio should be received with great skepticism. In small minority of cases there are well describ autopsy data which justify positive statemen regarding the origin of the arterial obstructio While I had intended to list the etiologic factor each case appearing in the table, enough eviden was seldom forthcoming to enable me to make statement on this point with accuracy.

Various pathogenic processes may be di cussed.

1. Sepsis has frequently been described as cause of arterial occlusion in young subject Overwhelming infection in infants is known give rise to multiple areas of cutaneous and dee tissue necrosis, particularly on the hands, the fe and the scalp and around the breast. In gener these lesions are relatively small, and in essen they represent focal areas of cellulitis or absce formation secondary to bacteremia. In such ci cumstances, the vascular changes are confine to relatively small vessels and are a part of th regional inflammation. Occlusion of large vesse occurs with rarity unless the heart has end cardial vegetations, some of which become di lodged and are carried into a part of the arteri tree. In either type of case—that in which sca tered necroses result from pyemia or that which major embolism arises from an infecte cardiac vegetation—the evidence of generaliz and severe sepsis should be unmistakable. febrile course, a general picture of great toxicit pronounced leukocytosis and, finally, positiv

Author and Year	Age of Patient at Onset of Symptoms	Part Involved; Nature of Involvement	Result
Martini: Mag. f. d. ges. Heilk. **27**: 423, 1828..	8 days	Gangrene of both lower legs	Death on 24th day
Klob,[12] 1859	8 days	Mesentery	Death
Rauchfuss,[15] 1859	10 days	Kidney	Death
Rauchfuss,[15] 1859	2 wk.	Lungs	Death
Ahlfeld, cited by Leopold, 1876	9 days	Necrosis, lateral side of right calf	Amputation of leg; patient died next day
Leopold: Arch. f. Gynäk. **10**: 189, 1876	15 days	Gangrene of both feet	Death on 18th day
Lüttick: Arch. d. Heilk. **71**: 70, 1876	14 days	Legs	Death
Welchert, cited by Leopold, 1876	10 days	Gangrene, both lower legs	Death
Durante: Méd. inf. **2**: 222, 1898	17 days	Both feet	Death a few days later
Durante, 1898	24 days	Gangrene, lower part of abdomen and upper parts of legs	Death a few days later
Freund, H. W.: Verhandl. d. deutsch. Gesellsch. f. Gynäk. **8**: 500, 1899	Newborn	Gangrene, left hand	Death on 8th day
Mueller,[8] 1899	1 day	Left forearm	Surgical amputation; death
Bronson,[7] 1902	1 day	Gangrenous areas on cheek, ear, neck, clavicle and thumb on right side	Part of ear sloughed away
Cotes-Preedy, D.: Lancet **1**: 575, 1904	Few days	Gangrene, right foot	Death on 14th day
Gruner,[11] 1904	5 wk.	Celiac artery	Death
de Bruin, J.: Nederl. tijdschr. v. geneesk. **2**: 1349, 1906	Newborn	Right leg	Autoamputation in a few weeks
Foltanek: Mitt. d. Gesellsch. f. inn. Med. u. Kinderh. **5**: 191, 1906	8 days	Foot	Recovery (?)
Wagener,[16] 1907	2 mo.	Lung	Death
Winslow, R.: Tr. South. Surg. & Gynec. A. **24**: 208, 1912; South. M. J. **5**: 48, 1912	3 days	Right forearm	Surgical amputation; recovery
Wieland, E.: Deutsche Ztschr. f. Chir. **116**: 783, 1912	2 wk.	Distal phalanx of 2 fingers of right hand	Tips of fingers sloughed away
Fitzwilliams, D. C. T., and Vincent, W. H.: Lancet **1**: 753, 1913	10 days	Lateral part of lower right leg	Surgical amputation
Kowalski,[13] 1921	5 days	Kidneys	Death
Löwy, L.: Mitt. d. Gesellsch. f. inn. Med. u. Kinderh. in Wien **21**: 152, 1922	5 days	Distal part of toes	Decovery
Castana, V.: Pediatria **31**: 1305, 1923	Newborn	Toes, lower part of left arm and hand	Loss of forearm; recovery
Hoopman and Grant,[6] 1924	11 days	Both feet	Death
Barmwater, K.: Wien. klin. Wchnschr. **38**: 220, 1925	Newborn	Gangrene, both hands and lower parts of both legs	Death on 9th day
Grove, W. R.: Brit. M. J. **1**: 738, 1926	7 days	Right foot	Loss of toes; recovery
DeSnoo, K.: Nederl. tijdschr. v. geneesk. **2**: 3915, 1928	8 days	Dorsum of heel and internal malleolus	Eventual disappearance of gangrene
Fischer, W.: Arch. f. Gynäk. **136**: 181, 1929..	7 days	Right hand and forearm	Death on 14th day
Obadalek, W.: Arch. f. Kinderh. **90**: 111, 1930	14 days	Left leg, from knee down	Surgical amputation
Grassi, A.: Riv. di clin. pediat. **29**: 120, 1931..	3 days	Right forearm	Autoamputation on 37th day; recovery
Lawrence, R. D., and McCance, R. A.: Arch. Dis. Childhood **6**: 343, 1931	15 days	Gangrenous areas on foot, wrist and buttock	Recovery in 11 wk.; temporary diabetes
Bettinger,[10] 1932	10 days	Lungs	Death
Corret, P.: Levy, and Beau: Rev. méd. de l'est. **60**: 64, 1932	12 days	Gangrene, lower leg	Surgical amputation; recovery
Dohan,[1] 1934	19 days	Gangrene, left leg and foot	Surgical amputation
Hallé, J., and Leveuf, J.: Bull. Soc. pédiat. de Paris **32**: 523, 1934	4 days	Dorsum and toes of right foot	Recovery
Barbé, P.: Bull. Soc. pédiat. de Paris **37**: 45, 1939	18 days	Six fingers	Death
Huber, J.; Florand, J., and Payet, M.: Bull. Soc. pédiat. de Paris **37**: 54, 1939	21 days	Tips of two fingers, each hand	Some sloughing; recovery
Levy, G.: Am. J. Dis. Child **62**: 381 (Aug.) 1941	1 day	Gangrene in right gluteal region	Spontaneous healing
Levy, 1941	9 days	Left leg	Surgical amputation; recovery
Heller and Alvarí,[5] 1941	1 day	Right forearm	Recovery
Gross, 1945	1 day	Left foot	Spontaneous amputation; recovery
Gross, 1945	1 day	Right hand and forearm	Complete recovery
Gross, 1945	7 days	Left foot and lower leg	Some sloughing; fair recovery
Gross, 1945	2 days	Both legs	Death
Gross, 1945	13 days	Brain, kidneys, lung, legs	Death
Gross, 1945	13 mo.	Brain, kidneys, legs	Death

blood cultures should make it clear that any development of gangrene would most certainly come from an underlying and grave infection. I have chosen to exclude most cases of this type from the present review and discussion in order to focus attention on arterial embolism and thrombosis which arise by other, and less well known, mechanisms.

2. Congenital heart disease is occasionally responsible for release of emboli into the blood stream, with consequent obstruction of arteries in either the pulmonary or the peripheral circuit. Sterile vegetations can form on a stenotic (or anomalous) valve; thrombi can appear on a chamber wall when there is fibrillation (Hoopman and Grant [6]); spontaneous clotting can occur in a heart when the coagulation mechanism is altered by the polycythemia of a cyanotic state. Under each of these conditions emboli can be dislodged into the circulating blood stream and can be carried to any artery, with disastrous results. The occlusion thus produced may be partial or complete; the destruction of tissue can be slight or irreparable. Unfortunately, embolism in such cases almost certainly carries a fatal prognosis, for whether the initial insult be mild or correctable, it will most likely be followed by embolism in other parts of the body. Those vascular accidents which are secondary to cyanotic forms of congenital heart disease can be seen at any age, but they are most prone to occur after an infection of the respiratory tract, gastroenteritis, fever, or other illness which induces dehydration, and thereby leads to hemoconcentration and augmentation of the blood coagulation.

3. Trauma has occasionally been mentioned as cause of thrombosis in one of the extremities or of necrosis of some external part of the body. Various types of pressure injury could conceivably be incriminated. Such accidents as constriction from an encircling umbilical cord (Bronson [7]), prolapse of an arm alongside the head in a birth canal (Mueller [8]) or undue pressure on a part during difficult delivery could possibly initiate vascular disturbances or gangrenous processes of serious degree. However, the frequent occurrence of such injuries and the contrasting rarity of gangrene in newly born babies certainly do not suggest any causal relationship between the two conditions. In the case Lawrence and McCance [9] there were isola gangrenous areas on a foot, a wrist and b buttocks. The child had temporary diabetes a no evidence of infection. The cutaneous chan were stated to be due to regional pressure nec sis, but no clearcut reason for this assumpti was given. It is my belief that, except in unus circumstances, trauma has little or nothing to with the arterial lesions which are here describ

4. Particular attention should be called to t ductus arteriosus, since thrombi may arise fr it which can be thrown off into the circulati blood stream and thus enter the pulmonary fie and most portions of the peripheral arterial c cuit. In a high percentage of human beings, t ductus arteriosus closes shortly after birth, a its obliteration is brought about by contracti scarring, degeneration and angulation in such way that local clotting of blood does not occ However, in some persons the closure is acco panied with thrombosis of the entire lumen with formation of a clot on each end of the othe wise obstructed vessel. It is obvious that portio of such a thrombus can break off and be carri away in the nearby streams of blood. All are of the pulmonary bed are subject to this haza of embolism. In addition, almost all of t peripheral vascular bed is in similar dange since clots can descend the aorta and can pro ably enter the left subclavian and left comm carotid arteries. It is not impossible, but it highly improbable, that they would enter the i nominate artery. Such clots, while initially rather small size, can produce widespread dama because their lodgment in any vessel is follow by propagation of the thrombus, both distal an proximal to the point of lodgment. Embolism a arterial obstruction of this kind can be min and remediable; conversely, the embolism can massive, multiple and fatal. The production pulmonary or peripheral embolism from a cl in the ductus arteriosus was encountered in m fifth and sixth cases. It likewise occurred cases reported by Bettinger,[10] Gruner,[11] Klob Kowalski,[13] Lüttick,[14] Rauchfuss [15] (2 cases

6. Hoopman, F. W., and Grant, R. L. T.: An Unusual Case of Gangrene of the Feet Occurring in an Infant, M. J. Australia **1**:288, 1924.

7. Bronson, E. B.: A Case of Gangrene in a New Born Child, Tr. Am. Dermat. A. (1901), 1902, p. 158.

8. Mueller: Ueber Gangrän von Extremitäten bei Neugeborenen, Inaug. Dissert., Strassburg, C. & J. Goeller, 1899.

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12. Klob, J.: Thrombosis Ductus Botalli, Ztschr. k. k. Gesellsch. d. Aerzte zu Wien **15**:4, 1859.

d Wagener.[16] It is my opinion that such a uence would have been found in a much ger number of cases if autopsy had been rmitted or if a more thorough postmorten amination had been performed.

Production of peripheral vascular accidents thrombi dislodged from the ductus arteriosus urs almost always, but not exclusively, in the st few weeks of life. Since thrombosis at the e of the ductus is most likely to occur at the ne of its obliteration, the incidence is largely nfined to the newborn period. (It is only with eat rarity that a clot arises in the ductus in der patients but instances of this condition have en described by Jager[17] as occurring at 55 ars, and by Altschule,[18] at 57 years.) It is vious that a closed or plugged ductus arteriosus ll not give rise to a murmur. Thus, embolism n originate from the cardiac area, and yet e heart will be normal by all physical signs.

5. Finally, another mechanism giving rise to rombosis in the arterial system is concerned th the transformation of the umbilical arteries m their fetal to their postnatal state. While e placental circulation is intact, blood flows wn the aorta, through the common iliac arteries d thence through the two hypogastric arteries, hich continue as the paired umbilical arteries. e umbilical artery (on either side of the pel-) courses alongside the bladder and rises on e inner aspect of the anterior abdominal wall gain entrance to the umbilical cord. When the ild is born and the placental circulation is shut , the long segment of each umbilical artery, m the inner aspect of the navel to its respective pogastric artery, becomes thrombosed and dergoes degenerative changes. Such throm- sis does not ordinarily extend beyond the functionalized segment, but it is possible for to extend up (against the blood current) into e hypogastric artery or even beyond, into the mmon iliac artery. By this retrograde progression, a thrombus may extend even into the lower portion of the aorta (fig. 4). It is obvious that any such thrombosis beyond the normal range can lead to serious interruption of arterial blood supply to one or both legs. A careful autopsy in my fourth case gave convincing evidence of this series of events leading to extreme gangrene of both lower legs. It is highly probable that less severe forms of this process have gone unrecognized; partial blocks of the common iliac artery or dislodgment of a small embolus into one of the smaller vessels of the leg could give rise to less extensive injuries. Certainly for any baby with arterial obstruction in one or both legs and without evidence of arterial occlusion elsewhere, the physician should clearly bear in mind the possibility of such a sequence of pathologic events.

13. Kowalski, W.: Ueber Thrombose des Ductus teriosus bei Neugeborenen, Virchows Arch. f. path. nat. **233**:191, 1921.

14. Lüttick: Zwei praktisch wichtige Gefassanomalien, rch. d. Heilk. **71**:70, 1876.

15. Rauchfuss, C.: Ueber Thrombose des Ductus teriosus Botalli, Virchows Arch. f. path. Anat. **17**: 6, 1859.

16. Wagener, O.: Thrombenbildung am durchgängigen uctus arteriosus (Botalli), Deutsches Arch. f. klin. ed. **89**:625, 1907.

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TREATMENT

The treatment of ischemia resulting from arterial thrombosis or embolism must vary with the extent of the lesion, the presence or absence of secondary sepsis, the degree of toxicity of the patient, the possible coexistence of similar lesions elsewhere in the body and the evaluation of any existing cardiac disorder.

Whenever an infant has impaired blood supply to an extremity, immediate precautions should be taken to prevent a superimposed secondary infection. The part should be widely cleansed with 70 per cent alcohol, a 1:1,000 solution of zephiran chloride or some bland antiseptic to remove surface bacteria. Then the entire area should be thoroughly encased in a sterile bandage, which should be adequately attached so that it will not be pulled or kicked off the baby. This dressing should be removed once or twice a day; there is little advantage in changing it more often. Too great stress cannot be placed on establishment of an aseptic technic in caring for the injured limb, for prevention of secondary infection greatly simplifies the physician's problem. If infection can be kept out of the picture, it is possible that a severely damaged limb might survive with a greatly reduced blood supply, whereas the combination of ischemia and infection almost certainly would lead to gangrene and extensive loss of tissue.

In no circumstances should heat be applied to an extremity with a damaged arterial blood supply. At ordinary room temperature the ischemic extremity may survive, but if its oxygen demands are increased by raising its temperature, the arterial system may not be able to meet the increased needs, and gangrene may result. Furthermore, fairly good reasons could be advanced

for artificially lowering the temperature of a damaged extremity. Certainly, the encasing of a part in ice (over sterile bandages) would reduce its oxygen requirement, and this treatment may be sufficient to permit its survival until the time when collateral circulation can be improved and give more adequate nourishment to the part. Ice packs were used on an injured leg in my third case. Whether or not this treatment contributed to the ultimate survival of the limb is open to question, but the theoretic considerations and the happy outcome make me enthusiastic about advising its further trial in other cases. In short, an ischemic limb should not be artificially heated; it is wise to leave it at room temperature. If sufficient nursing care is available, it is probably best to keep the part in an ice pack for several days.

Inspections of the limb at twelve hour or twenty-four hour intervals are sufficient to permit an accurate appraisal of the state of the local circulation. While examination after the initial insult might indicate widespread coldness, pallor or cyanosis, subsequent observations may show that only a relatively small distal part of the affected area will be demarcated and headed for subsequent necrosis. As long as the baby shows no serious signs of toxicity, a period of watchful waiting is in order, because what at first appears to be an extensive area of injury, necessitating radical amputation, may subsequently prove to be a rather minor area of gangrene, which requires but a simple operative excision. Indeed, in favorable circumstances, actual tissue necrosis may not appear at all and surgical procedure will not be required. Amputation should rarely be an emergency procedure. Obviously, if infection is extensive or if the toxicity of the patient is great, surgical removal of the limb can be a life-saving procedure. However, in most instances there is little need for haste, and a judicious deferment of operation is usually advisable. In some cases autoamputation results in the least possible loss of substance. Adoption of these principles in my first case has certainly left a foot with more remaining substance than would have been the case if early operation had been resorted to and all apparently damaged substance had been removed.

The circulation of an ischemic limb can be temporarily improved to some degree by blockage of its sympathetic nerve supply with procaine. This treatment permits maximum dilatation of collateral arteries and arterioles. In my third case injections of procaine hydrochloride into the lumbar portion of the left sympathetic chain were repeated for four days, and there was definite improvement in the circulation of the leg for several hours after each of these tr ments. The technic of sympathetic blockage infants is not difficult if the physician has a r sonable familiarity with the local anatomy if he has had previous experience with such p cedures in older patients. The injection sho be repeated every six or eight hours for two three days, or until it is evident that the limb survive without further repetition of the tr ment.

From a theoretic point of view, the introd tion of anticoagulants into the circulating bl would probably have some beneficial effects babies with arterial obstruction. Heparinizat would in no way alter an existing thrombus embolus, but it could temporarily limit its pro gation. The possible advantages are great, the difficulties of continuous (or frequent) int vascular administration of heparin to a sm subject for a considerable period seem to p clude the use of this drug as a therapeutic age

If sedation is necessary, it is probably advisa to use papaverine hydrochloride because of t vasodilator action which this drug possesses.

In conclusion, a thoroughly conservative po of view should be maintained in the treatment ischemia of the extremities in babies. A proc which at first may seem hopeless can often turned into one in which there is little or no l of substance. A review of the second case he reported certainly shows the advantage of period of expectant treatment. When the ch was first seen in consultation, amputation w strongly considered because of the coldness, t cyanosis and the complete flaccidity of the fo arm and hand. It was about ten days before could be sure that the part would be viable. was several weeks before any muscular functi returned. It was about five months before sho ening of the muscle was overcome and full mu cular power restored. It was nearly one ye before any pulsation could be felt below t elbow, but the child now has an arm and a ha which are normal in every way (fig. 2). Lik wise, in my third case a conservative attitude h been thoroughly justified. Some necrosis of sk appeared, but there has been spontaneous healin the muscular power has been gradually returni but is at the time of writing still slightly deficien no arterial pulsations could be felt until more th a year had elapsed. The child's left leg is not well developed or so strong as the normal, rig one, but functionally it is very useful.

SUMMARY

A study was made of 47 patients, including of my own, who had arterial thrombosis or e

ism in early life, principally in the neonatal riod. The origin of the occlusion was often scure, but in some cases it was apparently used by trauma, infection, embolism from ptic cardiac vegetations or abnormal clotting the presence of polycythemia. I should particularly like to draw attention to two additional chanisms whereby arterial vascular accidents be produced in babies. With the first, the rombosis of the umbilical arteries extends beyond the expected normal range so that the clot tends into the pelvic arteries or into the lower rtion of the aorta. With the second, a closing ctus arteriosus may be the seat of thrombus rmation, from which emboli can be thrown off o the pulmonary or the peripheral circuit.

In infants, arterial obstruction was found in brain, the kidneys, the mesentery, the lungs, arms and, especially, the legs. The prognosis many of these subjects is serious: One half of patients in the series died. Fatalities which secondary to cardiac disorders will probably always be unavoidable, but deaths from secondary sepsis can often be prevented by adequate care of an affected limb, by use of sulfonamide compounds and penicillin, and by amputation when necessary.

It is important to note that ischemia of an extremity does not necessarily mean that the part will die or that early amputation will be required. Occlusion of a large artery may at first seem incompatible with survival of the limb, but experience has shown that the collateral vessels of a baby have an extraordinary capacity for maintaining the blood flow. Hence, amputation should be deferred as long as is expedient; secondary infection should be carefully prevented, and every effort should be made to augment the impaired circulation. If an ischemic limb can be tided over its period of initial insult, there is a fairly good chance that it will survive and will regain satisfactory function.

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PATHOGENESIS OF NEPHROTIC HYPERLIPEMIA

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The purpose of the experiments reported herein was to study the endogenous mechanism which controls blood lipid concentration and to obtain knowledge which might explain the mechanism which increases the blood lipids in "lipemic nephrosis."

The endogenous origin of the hyperlipemia of nephrosis is shown by the fact that the condition is not affected by exogenous lipids.[1] It is also known that this increase in lipids is not due to a disturbance in the oxidation of fat.[2] The two hypotheses which try to explain the pathogenesis of the hyperlipemia of nephrosis (*a*) on the basis of the hypoproteinemia[3] and (*b*) as a primary disturbance of lipid metabolism[4] are insufficiently supported by experimental or clinical evidence.[5] Observations on children suffering from nephrosis suggested that the kidneys may exert some regulating influence on the blood lipid concentration and that nephrotic hyperlipemia may result from a disturbance of this mechanism. In favor of this hypothesis is the finding that an increase in blood cholesterol concentration follows total or partial nephrectomy or ureteral ligation in cats[6] and rats.[7]

In order to test this hypothesis, the total lip total and free cholesterol and phospholipid c centrations were determined in the blood serum dogs, rabbits and rats which were subjected bilateral and unilateral nephrectomy or to ente and parenteral administration of mercury chloride, uranium nitrate and potassium dich mate. For control purposes, the effects of spl ectomy, cholecystectomy, sham operations a many other procedures were also investigated.

METHODS

All determinations were made on serum. Choleste analyses were made according to Schoenheimer a Sperry's method,[8] which had been adapted to use w a photoelectric colorimeter. The total lipid con was analyzed according to the gravimetric method Wilson and Hanner[9]; phospholipids were determin after extraction according to the technic of Bl with the method of Benedict and Theis,[10] and w calculated as lecithin; serum proteins were determi according to Kingsley's method.[11]

From all animals 10 cc. of blood was obtained 9 a. m. As will be discussed later, it was found t the withdrawal of food and water, even for seve days, did not detectably affect the blood lipid c centration in dogs fed dog chow. Consequently, animals were not made to fast previous to the wi

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wal of blood. After the operations the dogs were urned to their cages and were given food and ter, except those which had been subjected to bilateral hrectomies.

The dogs were maintained on a Dog Chow ration l were fed bones once a week. The rabbits (3,500 4,000 Gm.) were kept on a diet of oats, hay, cab- e and carrots. The rats (150 to 275 Gm.) were Sherman's standard mixture.

The operations[12] were performed with the dogs ler morphine-ether anesthesia. Nephrectomies were e extraperitoneally. Sham splenectomies and sham hrectomies were carried out in all details, including manipulation of kidney or spleen, without, how- r, removing the tissue. Extensive cauterization carried out with the dogs under ether anesthesia, g a red hot metal plate 1½ inches (3.8 cm.) in th and 3 inches (7.6 cm.) long. The incision in skin was sutured following both subcutaneous intramuscular cauterization. After it had been blished that certain operations and injections did affect the results of subsequent studies, the same mal was occasionally used for different experiments r it had completely recovered from the previous ration.

Oral administration of mercury bichloride was tried tube and by enveloping mercury bichloride powder an enteric coated pill containing mercury bichloride a thick slice of steak. Because these precautions not prevent vomiting, mercury bichloride had to injected into the upper part of the jejunum in arotomized animals.

The kidney extracts were obtained by extracting m 10 to 12 Kg. of finely ground, fresh kidney, ssly free from fat, with 12 to 15 liters of 2 per t sodium chloride. After a few crystals of thymol glacial acetic acid had been added and a p_H of to 4.7 had been obtained, the extract was vigorously red for one to two hours and allowed to stand in ice box overnight. It was then freed from the k of insoluble residue by squeezing through cheese- th. The precipitate, which formed overnight and ile concentration *in vacuo* at a low temperature s carried out, was removed by centrifugation or fil- ion. After being dialyzed against running tap er for fifteen to twenty-four hours, the extract was in concentrated *in vacuo* to the desired volume and atted by four or five extractions with ether.

RESULTS OF EXPERIMENTS

Nephrectomy.—Bilateral nephrectomy, per- med on 3 dogs, led without exception to a ntinuous rise of the serum cholesterol content to the time of death (chart 1). The increase total lipids was greater than that in cholesterol. Unilateral nephrectomy was performed on 6 gs. It was found that this operation was fol- ved regularly by a rise of cholesterol, phos- olipids and total lipids (chart 2). This hyper- emia reached its peak within two to eight days er the operation and values returned to nor- l from six to fourteen days after one kidney had been removed. It is noteworthy that this result was obtained without exception.

Fasting and Anesthesia.—In order to clarify the possible significance of factors other than removal of renal tissue which might be involved in bringing about these results, we first studied the influence of prolonged omission of food and water. This was done on 5 dogs for two to fifteen days, with negative results. We then investigated the influence of forty-five minutes of anesthesia on serum lipids in 4 dogs. One-half grain (0.03 Gm.) of morphine sulfate was given one-half hour before ether was administered. The animals were not made to fast before or after narcosis. In 1 dog there was a slight rise, and

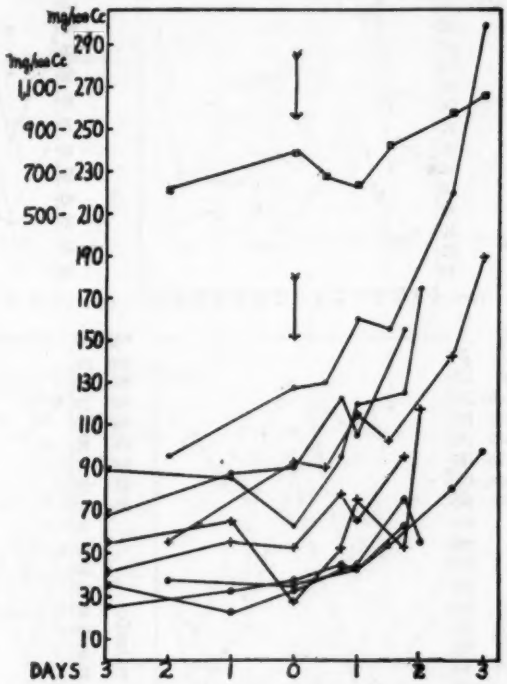

Chart 1.—Increase in total lipids and cholesterol in serum after bilateral nephrectomy (arrow) in 3 dogs.

In this figure, and in the accompanying figures, the line with squares indicates values for total lipid; the line with small black circles, values for cholesterol; the line with crosses, the values for cholesterol ester, and the line with hollow circles, values for free cholesterol.

in another a definite temporary rise, in total lipids without involving cholesterol or phospholipids. In the 2 remaining dogs all lipid values remained unchanged. Anesthesia in itself may consequently be occasionally responsible for a postoperative increase in total lipids. Under the prevailing conditions of our experiments, however, we feel certain that the rise in cholesterol and lecithin produced by bilateral or unilateral nephrectomy could not be due to fasting or to the anesthesia. The regularity with which the

2. Dr. Harry Goldblatt, of the Institute of Pathol- y, Western Reserve University School of Medicine, formed the operations on the dogs, made the histologic aminations of the kidneys and obtained blood from ypertensive dogs.

total lipids participated in the postnephrectomy hyperlipemia also made it certain that anesthesia alone cannot be responsible for this rise.

Sham Nephrectomy and Sham Splenectomy.—Sham nephrectomies were performed on 3 and sham splenectomies on 2 dogs. One animal of 5 fifth dog no change of cholesterol, phospholip or total lipid values was observed. In brief, on one of five sham operations caused postoperati hyperlipemia comparable in pattern and intensi to the reaction observed regularly after nephre tomy.

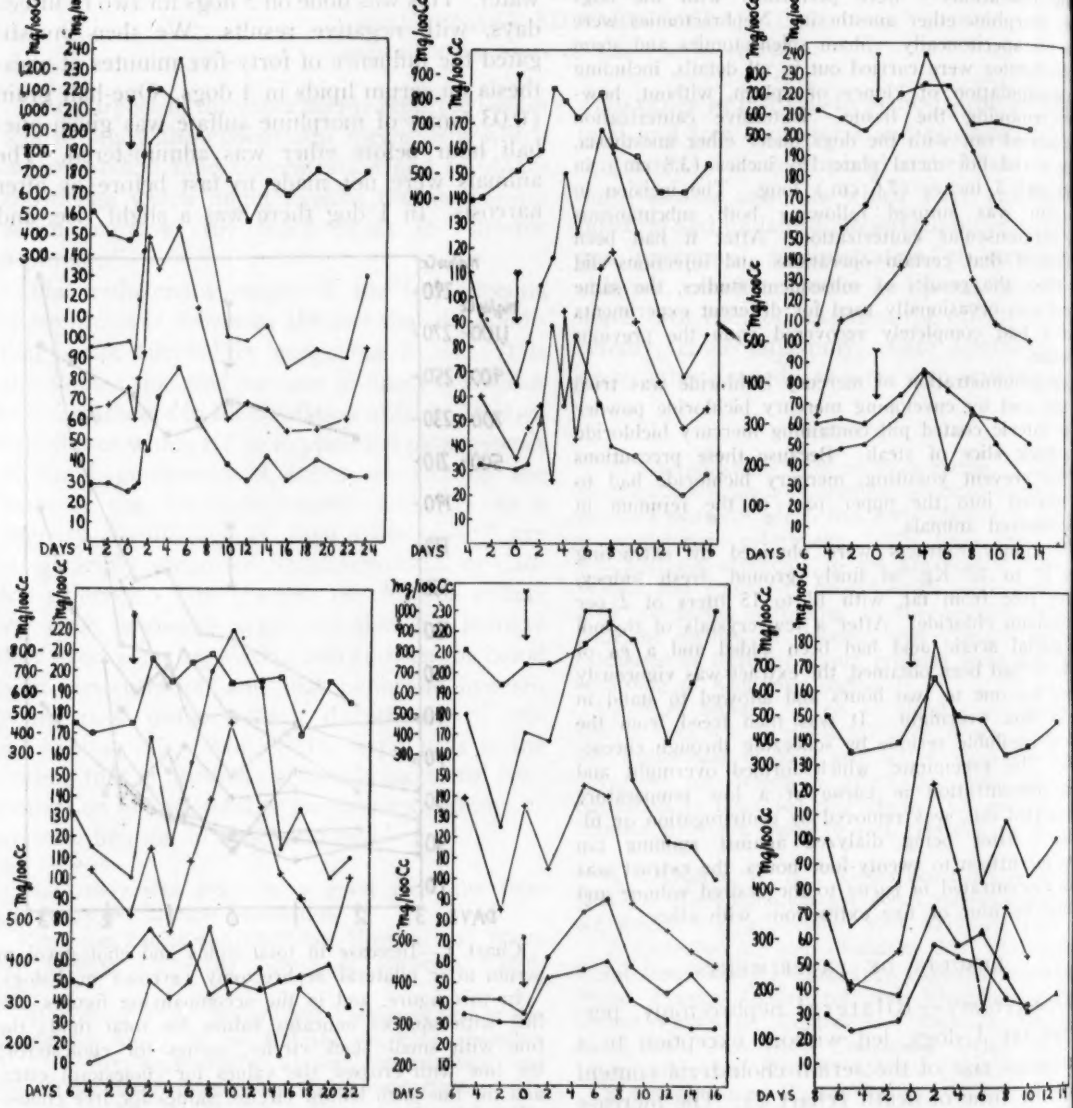

Chart 2.—Temporary hyperlipemia, involving total lipids, cholesterol and phospholipids, after unilater nephrectomy (arrow) in 6 dogs.

In this figure, the line with small triangles indicates values for lecithin.

showed postoperative hyperlipemia, involving all three lipid fractions examined. This reaction was indistinguishable from that observed after nephrectomy. In 2 other dogs only the total lipids rose temporarily, a change which may have been due to the anesthesia. A fourth dog showed only a slight increase of phospholipids of short duration, without a corresponding increase in total lipid and cholesterol values. In the

Cholecystectomy and Splenectomy.—Furth control experiments were carried out, 3 dog being subjected to cholecystectomy and 5 t splenectomy. Removal of the gallbladder result in a slight rise in serum cholesterol, without co responding changes in total lipids or in lecithi in only 1 dog. In the other 2 the serum lipid were not changed. In 3 dogs removal of th spleen was followed by temporary hyperlipemi

volving total lipids, cholesterol and phospho-
ids. In 2 of these dogs the changes were less
ensive and less regular than those following
phrectomy; in the third dog the postoperative
perlipemia was of considerable degree, the rise
d fall of the curve being identical with the
perlipemia following unilateral nephrectomy.
lenectomy in the fourth animal was followed by
with those of unilateral and bilateral nephrec-
tomy.

Nephrotoxic Chemical Agents.—In attempting to clarify the nature of postnephrectomy hyperlipemia, it was thought advisable to study the effect which nephrotoxic chemical agents might have on blood lipids in dogs. Mercury bichloride was the first agent studied. An oral dose of 0.5

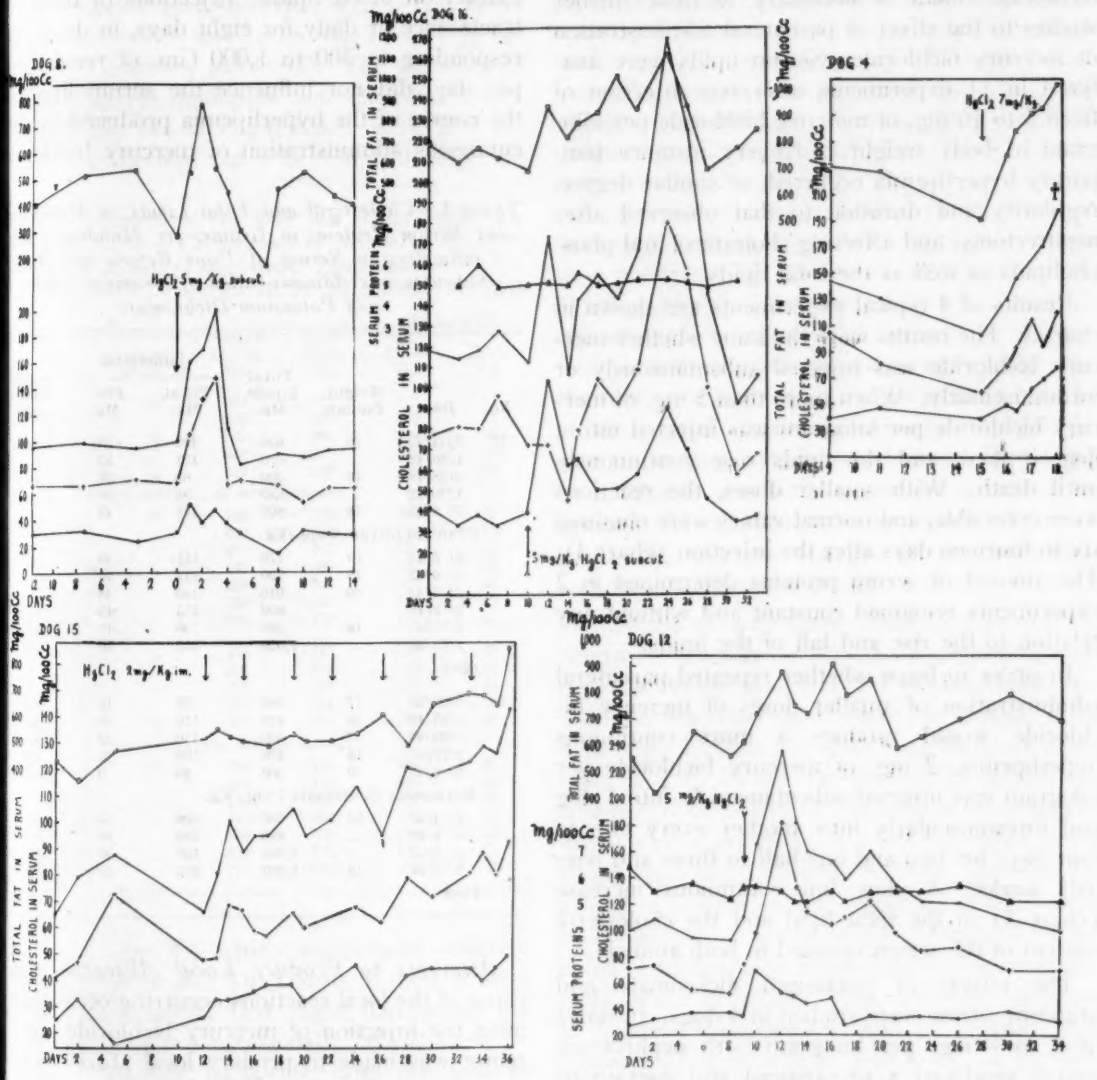

Chart 3.—Temporary hyperlipemia in 5 dogs after single and repeated parenteral administration of mercury chloride.

In this chart, the line with small triangles indicates values for serum protein.

slight increase of serum cholesterol and phos-
olipids without appreciably involving the total
ids. The fifth dog showed only a rise in total
ids, without any simultaneous increase of
ithin or cholesterol value. Splenectomy more
en than any other control operation caused
mporary hyperlipemia. The results did not
mpare, however, in regularity and intensity
to 3.0 Gm. was vomited sooner or later almost regularly in whatever form we tried to give it. Consequently, the actual amount retained is unknown. The results of 6 experiments on 3 dogs were inconclusive. There was no great elevation of total lipids or cholesterol, even though some delayed and irregular, slight hyperlipemia may have been produced. Because of the vomiting, mercury bichloride was injected into the

upper part of the jejunum of 3 laparotomized animals. Temporary hyperlipemia occurred in all, involving the three lipids which were being examined. The reaction started within two to fourteen days and lasted from five to over twenty-four days after operation.

The coexistence of two complicating factors in these last experiments—operation and mercury bichloride—made it necessary to limit further studies to the effect of parenteral administration of mercury bichloride. Serum lipids were analyzed in 11 experiments after one injection of from 5 to 16 mg. of mercury bichloride per kilogram of body weight. In every instance temporary hyperlipemia occurred, of similar degree, regularity and duration to that observed after nephrectomy, and affecting cholesterol and phospholipids as well as the total lipids.

Results of 4 typical experiments are shown in chart 3. The results were the same whether mercury bichloride was injected subcutaneously or intramuscularly. When more than 5 mg. of mercury bichloride per kilogram was injected into a dog, it died, and the lipids rose continuously until death. With smaller doses, the reactions were reversible, and normal values were obtained six to fourteen days after the injection (chart 3). The amount of serum proteins determined in 2 experiments remained constant and without any relation to the rise and fall of the lipids.

In order to learn whether repeated parenteral administration of smaller doses of mercury bichloride would produce a more continuous hyperlipemia, 2 mg. of mercury bichloride per kilogram was injected subcutaneously into 1 dog and intramuscularly into another every two to four days for two and one-half to three and one-half weeks. A slow but continuous increase (chart 3) in the total lipid and the cholesterol content of the serum resulted in both animals.

The effects of potassium dichromate and uranium nitrate were studied in 4 dogs. In doses of 6 to 7 mg. per kilogram both nephrotoxic agents produced a pronounced and continuous increase in total lipids and serum cholesterol (table 1).

Non-Nephrotoxic Agents Administered Parenterally.—Since it had been determined that mercury bichloride, potassium dichromate and uranium nitrate produce the same kind of hyperlipemia as is regularly observed after unilateral or bilateral nephrectomy, it was thought necessary to have control experiments by studying the possible influence which various parenterally administered, non-nephrotoxic agents might have on the serum lipids of dogs. This seemed necessary because the three agents studied cannot be considered exclusively nephrotoxic. Another reason is that they occasionally caused abscesses and ulcers to 1½ inch (2.5 to 3.8 cm.) in diameter but no marked local inflammation at the site of the injection. One series of experiments can be considered controls, their original plan having been to investigate the action of beef or swine kidney extract on blood lipids. Injections of these extracts once or daily for eight days, in doses corresponding to 300 to 1,000 Gm. of renal tissue per day, did not influence the serum lipids or the course of the hyperlipemia produced by subcutaneous administration of mercury bichloride.

TABLE 1.—*Cholesterol and Total Lipids, in Milligrams, and Serum Protein, in Grams, per Hundred Cubic Centimeters in Serum of Dogs Before and After Subcutaneous Administration of Uranium Nitrate and Potassium Dichromate*

No.	Date	Weight, Pounds	Total Lipids, Mg.	Cholesterol		Serum Protein, Gm.
				Total, Mg.	Free, Mg.	
17	1/24/42	20	620	102	33	....
	1/26/42	..	620	121	53	....
	1/28/42	19	500	85	29	....
	1/30/42	..	640	84	58	....
	2/ 2/42	18	800	125	42	....
	Uranium nitrate 6 mg./Kg.					
	2/ 4/42	19	770	111	38	....
	2/ 6/42	19	720	114	40	....
	2/ 7/42	20	910	148	48	....
	2/ 9/42	..	900	155	45	4.55
	2/11/42	18	780	190	42	4.7
	2/13/42	..	1,020	225	59	6.8
	Died					
18	2/20/42	17	580	52	18	4.0
	2/23/42	20	420	110	30	4.0
	2/25/42	17	560	110	33	4.4
	2/27/42	18	470	100	33	4.7
	3/ 2/42	20	500	40	0	4.5
	Potassium dichromate 7 mg./Kg.					
	3/ 4/42	19	630	108	35	5.2
	3/ 5/42	..	820	150	40	5.5
	3/ 6/42	..	1,090	190	56	5.3
	3/ 7/42	18	1,600	216	39	5.5
	Died					

Attempts to Produce Local Abscesses.—Because of the local reactions occurring occasionally after the injection of mercury bichloride, an attempt was made to produce local abscesses and necrosis by subcutaneous and intramuscular injection of 10 cc. of 5 and 10 per cent calcium chloride and by subcutaneous and intramuscular cauterization. In 3 of 4 animals into which calcium chloride was injected, infiltrations causing abscess formation and ulceration developed. These local reactions were of somewhat greater intensity than those occasionally seen after injection of mercury bichloride. In 2 animals there was a questionable to slight increase of the phospholipids without corresponding elevation of either total lipids or cholesterol. In 1 there was a slight increase of cholesterol of short duration

ithout a corresponding rise in phospholipid or tal lipid values.

We then tried to obtain more intensive local ecrosis by cauterization. This was done subtaneously and intramuscularly, with the animals nder morphine-ether anesthesia. In 2 dogs the ecrosis was less intensive than in 2 others. The uterization in the last 2 dogs (table 2) produced cal necrosis of great severity, such as was never efore observed in any of the dogs receiving inctions of mercury bichloride. The elevation of tal lipids, phospholipids and cholesterol was egligible in the 2 dogs which were less insively cauterized but was definite in dogs 34

ABLE 2.—*Cholesterol, Lecithin and Total Lipids per Hundred Cubic Centimeters in Serum of Dogs Subjected to Extensive Cauterization*

No.	Date	Weight, Pounds	Total Lipids, Mg.	Lecithin, Mg.	Cholesterol	
					Total, Mg.	Free, Mg.
34	4/26/43	25	520	377	160	41
	4/28/43	..	480	370	140	41
	4/30/43	24	530	304	140	41
	5/ 3/43	..	370	350	104	33
	5/ 5/43	..	400	280	106	28
	Extensive cauterization, subcutaneous					
	5/ 7/43	26	740	420	182	87
	5/10/43	..	650	398	200	61
	5/12/43	23	420	342	172	53
	5/14/43	..	390	308	159	48
	5/17/43	..	580	262	125	38
	5/19/43	..	730	362	154	43
	5/21/43	..	760	372	177	58
35	4/26/43	..	470	347	140	47
	4/28/43	..	520	314	122	43
	4/30/43	..	600	370	112	43
	5/ 3/43	..	610	351	...	..
	5/ 5/43	20	560	308	128	43
	Extensive cauterization, intramuscular					
	5/ 7/43	18	780	427	200	60
	5/10/43	..	760	434	240	76
	5/12/43	..	470	342	159	53
	5/14/43	..	540	392	182	64
	5/17/43	..	670	362	172	42
	5/19/43	..	620	372	185	51
	5/21/43	..	770	302	177	67

nd 35 (table 2), which were more severely ffected by necrosis. The results in these control nimals demonstrate that slight damage to the ssues such as can occasionally be produced by njecting mercury bichloride, does not lead to yperlipemia. Severe tissue necrosis, such as was roduced by cauterization in dogs 34 and 35, ay, however, at least in combination with morhine-ether anesthesia, give rise to a temporary yperlipemia indistinguishable from the reaction aused by mercury bichloride.

This result induced us to produce severe local nflammations and abscesses without complicating heir possible effect by addition of ether anesthesia. This was done by subcutaneous and intramuscular injection of 3 to 10 cc. of oil of turpentine in 6 experiments, 2 to 5 cc. of croton oil in experiments and 8 to 10 cc. of carbon tetrachloride in 5 experiments. Oil of turpentine produced large abscesses without any significant interference with the general condition of the animal. In all 5 dogs a pronounced hyperlipemic reaction occurred, consistently involving cholesterol, phospholipids and total lipids. Croton oil produced equally large abscesses and proved to be much more toxic. Three of the 4 dogs receiving injections of croton oil died. The hyperlipemic reaction was especially pronounced in the animals which received intramuscular injections. Both animals which received injections under the skin showed some increase of serum cholesterol with irregular, but not pronounced, increase in the total lipids and the phospholipids. Carbon tetrachloride was used in 5 animals. It produced large abscesses without much general toxicity and was followed in 4 instances by temporary hyperlipemia, indistinguishable in extent and course from that observed after injection of mercury bichloride. One animal was selected from each group and the corresponding data recorded in table 3. Five of the animals that received oil of turpentine, croton oil and carbon tetrachloride were killed by inhalation of ether at the height of the hyperlipemia. Their kidneys were examined microscopically, but no change of unquestionably pathologic nature was found.

Experiments with Other Animals.—In order to determine whether or not administration of mercury bichloride and bilateral nephrectomy produce the described hyperlipemia in animals other than dogs, 7 rabbits received subcutaneous injections of 2 to 10 mg. of mercury bichloride per kilogram of body weight. In none of these experiments were there changes in the total lipid or the serum cholesterol content. Rabbits, however, are known to possess unique properties as far as their lipid metabolism is concerned. Therefore we decided to study this problem in rats. Fourteen animals served as controls. Six rats were subjected to bilateral nephrectomy, and 15 received subcutaneously injections of 3 to 8 mg. of mercury bichloride per kilogram. The nephrectomized animals showed on the average a questionable increase of serum cholesterol, and the group receiving injections of mercury bichloride showed a distinct elevation of serum cholesterol and total lipids (table 4). The effect of nephrectomy on rats is far from being as plain as that on dogs, and the hyperlipemia caused by injection of mercury bichloride is less intense. However, Ludewig and Chanutin [7] showed that in rats maintained on a different diet partial or total nephrectomy is doubtless followed by a rise in blood lipids.

COMMENT

It has been demonstrated that bilateral, as well as unilateral, nephrectomy in dogs regularly produced a progressive or temporary hyperlipemia, involving cholesterol, phospholipids and total lipids. This result cannot be explained as due to

TABLE 3.—*Cholesterol, Lecithin and Total Lipids per Hundred Cubic Centimeters in Serum of Dogs Receiving Injections of Carbon Tetrachloride, Oil of Turpentine and Croton Oil*

No.	Date	Weight, Pounds	Total Lipids, Mg.	Lecithin, Mg.	Cholesterol	
					Total, Mg.	Free, Mg.
26	12/28/42	32	580	528	100	27
	12/30/42	..	650	282	116	34
	1/ 5/43	..	690	300	65	22
	1/ 7/43	30	510	306	107	37
	8 cc. CCl_4 intramuscularly					
	1/ 9/43	26	940	566	230	141
	1/11/43	26	1,030	420	205	87
	1/13/43	..	620	359	205	70
	1/15/43	..	520	290	130	47
	1/18/43	..	640	310	170	53
	1/20/43	..	620	350	136	43
	1/26/43	31	670	310	140	42
	1/28/43	..	650	296	140	44
	2/ 1/43	..	540	354	112	51
	2/ 4/43	34	590	310	124	55
	8 cc. CCl_4 intramuscularly					
	2/ 6/43	29	720	442	200	91
	2/ 8/43	29	740	352	250	50
20	4/26/43	27	330	323	...	34
	4/28/43	..	390	324	100	28
	4/30/43	28	420	350	130	33
	5/ 3/43	..	520	360	153	43
	2 cc. croton oil intramuscularly					
	5/ 5/43	28	560	420	206	87
	5/ 7/43	..	740	407	200	83
	5/10/43	21	670	350	190	71
	5/12/43	19	700	392	260	92
	5/14/43	18	860	455	260	107
	5/17/43	15	520	372	207	92
	5/19/43	17	800	242	205	96
	Died					
24	12/28/42	20	580	268	100	31
	12/30/42	..	690	304	116	34
	1/ 5/43	23	690	298	83	22
	1/ 5/43	..	580	296	107	35
	5 cc. turpentine oil intramuscularly					
	1/ 9/43	21	870	470	200	124
	1/11/43	26	780	485	255	110
	1/13/43	20	930	400	245	102
	1/15/43	..	710	344	190	57
	1/18/43	20	480	294	100	37
	1/20/43	..	640	310	120	37
	1/26/43	21	470	274	116	32
	1/28/43	..	520	266	124	37
	2/ 1/43	24	460	340	116	..
	2/ 4/43	25	460	302	116	35
	5 cc. turpentine oil intramuscularly					
	2/ 6/43	21	920	452	240	120
	2/ 8/43	23	1,040	425	285	118
	Died					

starvation, thirst or anesthesia, even though the last-mentioned condition may sometimes have been responsible for a postoperative increase of the total lipids. Unknown factors connected with operations can, however, occasionally produce temporary hyperlipemia indistinguishable from the reactions observed after nephrectomy. This effect was observed once in 5 sham operations. More often, even though irregularly, it occurre after splenectomy, but in 3 dogs it did not occ after cholecystectomy. The kidneys, therefo seem to be involved in a mechanism which co trols blood lipid concentration. They are, ho ever, not the only known factor. The term "re hyperlipemia," used in a preliminary public tion,[13] does not imply an exclusive specificity f renal tissue.

This hyperlipemia is not restricted to dogs. has been observed in cats by Nekludow,[6] monkeys by Winkler and associates,[14] who al confirmed our results for dogs as far as bilater renal ablation is concerned, and in rats Ludewig and Chanutin.[7] Winkler, Durlache Hoff and Man [14] were, however, unable to co firm the results which we obtained after unilater ablation. These authors observed a rise in seru lipids after unilateral nephrectomy in 2 of 8 an mals and an increase in cholesterol only in 1 oth

TABLE 4.—*Average Values of Cholesterol and To Lipid, in Milligrams per Hundred Cubic Centimeters in Serum of Rats After Bilateral Nephrectomy and Subcutaneous Injections of Mercury Bichloride*

	Number of Animals	Total Lipid, Mg.	Cholesterol	
			Total, Mg.	Fre Mg
Controls	14	392	58	20
Bilateral nephrectomy (killed 24-76 hours after operation)	6	...	66	29
3-8 mg. $HgCl_2$ per Kg. subcutaneously (killed 2-4 days after injection)	15	465	102	36

animal. The fact that these authors used pento barbital sodium instead of morphine-ether anes thesia, as we did, does not explain this differenc because they also employed pentobarbital sodiu in the bilateral removal of the kidneys and foun the described hyperlipemia. It is possible, how ever, that Winkler and his associates missed th temporary elevation of the serum lipids in 5 dog for two reasons: 1. The normal fluctuation o total lipids, cholesterol and phospholipids induce us to make three or four examinations at leas before starting the experiment. These sample of blood were obtained from two to three day apart. With a few exceptions, these worker withdrew one sample of blood on the day o operation, which gave the only value that wa

13. Heymann, W.: Renal Hyperlipemia in Dog Science **96**:163-164, 1942.

14. Winkler, A. W.; Durlacher, S. H.; Hoff, E., and Man, E. B.: Changes in Lipid Content Serum and of Liver Following Bilateral Renal Abla tion or Ureteral Ligation, J. Exper. Med. **77**:47 486, 1943.

mpared with postoperative data. 2. The fact at they obtained the postoperative specimens of ood at irregular, and often too long, intervals [15] ay explain the difference in results. We also ubt that their observations after unilateral phrectomy on 2 monkeys (table 2, page 477) cluded the possibility of postoperative hyperemia in these animals. One basic value before eration compared with one obtained at an examination made seven days later might prove conclusive in more extended analyses. That e had more positive results after splenectomy an Winkler had in his studies may be explained the same facts.

Our conclusions as to the results obtained in olecystectomized animals agree with those of tkinson and Ivy.[16] Our results, however, cant be compared with theirs, because all of their gs were made to fast for three days before ch study of the blood lipid levels. As has ready been stated, our dogs were not made to st. This difference may be of great significance fat metabolism studies.

As far as we were able to determine, no data uld be found in the literature regarding the inence which nephrotoxic chemical agents may ve on blood lipids. Only one publication, by ichert, Jakowlewa and Pospeloff,[17] cites high olesterol values (414 and 540 mg. per hundred bic centimeters respectively) in the blood of 2 man beings with mercury bichloride poisoning.

We found that in dogs parenteral administraon of mercury bichloride, uranium nitrate and tassium dichromate regularly produced an inease in the serum of total lipids, cholesterol d phospholipids, which was temporary or conuous, depending on the dose given. This perlipemia developed without any decrease in rum protein content. This finding, in turn, es not give any support to the hypothesis [3] hich explains the hyperlipemia found in cases of phrosis by the hypoproteinemia. Hyperlipemia e to mercury bichloride was found not only in gs but in rats, whereas it was not observed in bbits. The negative results obtained with inction of calcium chloride or with moderate uterizations showed that the hyperlipemia was not due to the local irritation which mercury bichloride may occasionally cause. We believe that the hyperlipemia observed after injection of mercury bichloride, uranium nitrate and potassium dichromate is due to the renal damage they produce. The results obtained after renal ablation appear to justify this conclusion. It seems that in dogs, cats, rats and monkeys the kidneys are involved in a mechanism which influences blood lipid concentration. It also is certain, however, that the kidneys are not the only factor involved.

Severe necrosis and ulceration produced by extensive cauterization yielded results indistinguishable from those obtained after injection of mercury bichloride. We therefore believe that the extensive tissue necrosis and abscesses observed after injection of oil of turpentine, croton oil and carbon tetrachloride are sufficient to explain the temporary hyperlipemia which occurred after injection of these agents.

All further work as to the nature of this mechanism has thus far contributed only negative results. It is unlikely that the kidney produces some hormone-like substance which involves fat metabolism. Beef and swine kidney extracts had no effect on blood lipids of normal animals or on those of animals receiving injections of mercury bichloride. We would, therefore, revise a previously expressed opinion,[13] which suggested the subsequent hypertrophy of the remaining kidney as an explanation for the return of the hyperlipemia to normal values after unilateral nephrectomy.

Because recent work [18] has shown that there is intensive metabolism of phospholipids in renal tissue, which conceivably may be related to this problem, we compared the values for lipids obtained by analyzing blood from the renal vein with corresponding values for blood from the jugular vein and the femoral artery. No significant differences were found.

It is known that in cases of renal disease hyperlipemia is found when the tubular apparatus, rather than the vascular renal system, is affected. Accordingly, it was not surprising to find normal lipid values in the serum of 4 dogs which had been made hypertensive five weeks to four years previously by constriction of the renal artery.

On the basis of the results obtained in these experiments, we feel justified in suggesting the hypothesis that the hyperlipemia associated with nephrosis is of renal origin.

15. In 3 instances (table 1, page 474; dogs 1, 3 nd 4) the first postoperative examinations were made ight to ten days after the removal of one kidney at time, when hyperlipemic values may already have eturned to normal.

16. Atkinson, A. J., and Ivy, A. C.: Does Removal f Normal Gallbladder Affect Metabolism of Lipids? Lab. & Clin. Med. **23**:441-448, 1938.

17. Wichert, M.; Jakowlewa, A., and Pospeloff, S.: Organs in Mercury Poisoning, Ztschr. f. klin. Med. **01**:173-184, 1924.

18. Chaikoff, I. L.: The Appliance of Labeling Agents to the Study of Phospholipid Metabolism, Physiol. Rev. **22**:291-317, 1942.

SUMMARY

Bilateral and unilateral nephrectomy in dogs regularly produced an increase of total lipids, cholesterol and phospholipids in their blood serum. This increase was progressive after bilateral renal ablation and persisted for only one to two weeks after the removal of one kidney.

Abstinence from food and water and the anesthetics used did not produce such an increase.

No postoperative hyperlipemia was observed after three cholecystectomies; however, it was found after one of four sham operations and after three of five splenectomies.

Mercury bichloride given parenterally to dogs regularly produced an identical reaction, involving total lipids, cholesterol and phospholipids. The hyperlipemia so produced is independent of the serum protein concentration. After parenteral administration of uranium nitrate and potassium dichromate the same kind of hyperlipemia developed.

Inasmuch as parenteral administration of calcium chloride and mild cauterization of tissues did not cause a hyperlipemic reaction, it can be accepted that the hyperlipemia produced by injecting mercury bichloride, uranium nitrate and potassium dichromate was not due to the resultant local irritation.

Severe tissue necrosis produced by extensi subcutaneous and intramuscular cauterization a degree never before obtained after the pare teral administration of mercury bichloride di however, produce definite, temporary hype lipemia, of the same pattern as that found aft injection of the nephrotoxic agents.

Oil of turpentine, croton oil or carbon tetr chloride administered parenterally caused lar local abscesses and ulcerations. The degree the injury so produced presented an adequa explanation for the resulting hyperlipemia reg larly observed.

The same changes in blood lipids occurred rats after administration of mercury bichlorid but no changes were observed in rabbits aft similar injections.

Beef and swine kidney extracts did not infl ence the serum lipids either of normal dogs of dogs receiving injections of mercury bichlorid

It is concluded that the kidneys of dogs, cat rats and monkeys are part of a mechanism whi influences blood lipid concentration.

The hypothesis is advanced that the hype lipemia found in cases of nephrosis is of ren origin.

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DIAGNOSTIC CLASSIFICATION OF PATIENTS WITH MENTAL DEFICIENCY

DISTRIBUTION OF 1,330 INSTITUTIONALIZED PATIENTS, WITH REVIEW OF INCIDENCE OF CONVULSIVE DISORDERS AND NONCEREBRAL DEVELOPMENTAL ANOMALIES

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The central nervous system is probably the most vulnerable organ in the fetus and the newborn. Since mental deficiency is the most common manifestation of abnormality of the central nervous system occurring in the neonatal period, it would appear reasonable that a review of the etiologic diagnoses for a large number of persons with mental deficiency might throw light on the relative importance of the various factors that may play an injurious role in fetal and neonatal life. The purpose of this paper is to present a critical analysis of the etiologic diagnoses for 1,330 patients with mental defects.

MATERIAL AND METHODS

The patients studied represent all those admitted to the Southbury Training School, Southbury, Conn., since its inception, in October 1940, for whom a reasonably reliable diagnosis could be made on the basis of the available history and clinical study. The majority of the patients, roughly 70 per cent, were under 21 years of age. Approximately 2 per cent of the patients were less than 6 years old, the youngest being 3½ years old. Forty-nine per cent were between 6 and 16 years; 17 per cent, between 16 and 21 years; 15 per cent, between 21 and 30 years, and the remaining 17 per cent, over 30 years of age. The oldest patient was in her sixty-fourth year. The patients were equally divided as to sex.

In most of the cases the medical histories were obtained by a physician from the parents on the patient's admission. When this procedure was not possible, because of death of parents, illegitimacy, etc., it was necessary to rely on data available in the social service records or on information that could be obtained from other institutions or agencies which had at some time had contact with the patient. Inquiries were made of hospitals and clinics in which the child had been a patient at some prior time and the available information included in the record. Information concerning the parents or other siblings was obtained in a similar manner whenever this was available. For about 10 per cent of all of the patients admitted to the institution, the past medical record and the family history were considered too meager or inaccurate to be of significant value. These patients were not included in the present study. Facilities for complete laboratory and roentgenographic examinations were available and were utilized when such procedures were necessary. Pneumoencephalographic examination was carried out in a small percentage of cases but did not prove of significant assistance in reaching an etiologic diagnosis. Electroencephalography, while helpful in many respects, was not considered of significant value in the present study. All the patients were classified psychometrically by competent resident psychologists.[1]

It was possible to include all the etiologic diagnoses in thirteen categories. Some of these need definition. The diagnosis of familial defect was made when either one or both parents or other siblings showed evidence of a mental defect of similar character and degree to that exhibited by the patient. Congenital cerebral palsy was defined as a motor defect present at or appearing soon after birth and dependent on pathologic abnormalities in the brain which could not be attributed to known causes. In the majority of patients in this category the defect was a spastic diplegia, although cerebellar ataxia, atonic diplegia and certain of the hemiplegias were included. Epilepsy, per se, was considered the cause of the mental defect only if it could be shown that a normal mental state had existed prior to the onset of the convulsions and that gradual mental deterioration occurred in such a way as to indicate a causal relationship to the epileptic seizures. While many other children had convulsive states, the mental defect of the children in this category was considered either as being an associated symptom of the underlying disorder of the brain or as having no significant causal relationship to the mental defect. The category of craniofacial defects includes microcephaly, congenital hydrocephalus, premature synostoses of cranial sutures and hypertelorism. The diagnosis of microcephaly was made only in those cases in which not only the size but the configuration of the skull was characteristic. The size of the head alone is not a sufficient criterion to justify a diagnosis of microcephaly, since much greater degrees of smallness of the head are seen in cases of cerebral palsy than in cases of typical microcephaly. Cerebral lipoidosis includes varieties of Tay-Sachs disease (amaurotic family idiocy) and lipochondrodystrophy. The category "congenital ectodermosis" includes the three diagnoses of tuberous sclerosis, neurofibromatosis and cerebral angiomatosis. The category of undifferentiated defects includes the large group of conditions in which,

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1. Dr. Seymour Sarason and Mrs. Esther Sarason made the psychologic studies.

in spite of adequate histories and clinical study, a definite etiologic classification could not be found.

The classification of moron, imbecile and idiot was dependent on the results of psychometric examinations. Intelligence quotients were calculated on the basis of the 1937 Terman revision of the Binet test. For patients with severe physical disability and for patients with pronounced mental defect, the mental age was estimated roughly by other means. Children with intelligence quotients of 50 to 75 were listed as morons, of 20 to 50 as imbeciles and of less than 20 as idiots.

RESULTS

Table 1 lists the categories of etiologic diagnoses in descending order of their numerical importance. The two largest groups include the patients with the familial and the undifferentiated defects, which together made up almost 70 per cent of the total institutional population. The patients with congenital cerebral palsy and those with mongolism were approximately equal in number, each comprising about 7 per cent of the total. Trauma and cerebral infection accounted for approximately 7 per cent of the total number of patients. The mental deficiency of 32 patients (2.4 per cent) was considered a result of birth injury. Meningitis, of varying cause, but primarily meningococcic, was listed for 16 patients. Nonsuppurative encephalitis accounted for the defect in 32 patients, including 7 who had the epidemic variety, 10 in whom encephalitis developed during the course of pertussis and 1 in whom encephalitis followed measles. Syphilis of the central nervous system was found in 3 patients. A diagnosis of fetal toxoplasmosis as a cause of the cerebral abnormality was made for 1 patient. Although disseminated choroiditis occurred in 5 persons in the group of undifferentiated defects, in none of these patients was cerebral calcification found. Unfortunately, serologic tests were not available for aid in this diagnosis.

TABLE 1.—*Diagnostic Classification of Defects of 1,330 Patients Admitted to an Institution for Mentally Defective Persons*

	Moron	Imbecile	Idiot	Total	Per Cent
Familial defects	425	80	7	512	38.50
Undifferentiated defects	35	114	264	413	31.08
Cerebral palsy	17	26	56	99	7.44
Mongolism	2	62	28	92	6.92
Epilepsy	25	25	2	52	3.91
Infection	10	13	28	51	3.83
Trauma	7	15	20	42	3.16
Craniofacial defects	7	10	16	33	2.48
Phenylpyruvic amentia	1	2	9	12	0.90
Cretinism	2	2	3	7	0.53
Muscular dystrophy	5	0	1	6	0.45
Cerebral lipoidosis	2	1	3	6	0.45
Congenital ectodermosis	2	1	2	5	0.38
Total	540	351	439	1,330	

The group with craniofacial defects included 14 patients with microcephaly, 5 with congenital hydrocephalus, 8 with hypertelorism, 3 with oxycephaly and 3 with scaphocephaly. It is of interest that 3 of the 8 patients with hypertelorism showed evidence of congenital heart disease, which in 1 patient was of the cyanotic type.

TABLE 2.—*Distribution of Patients with Convulsive Disorder According to Diagnosis of Mental Defect*

	Moron	Imbecile	Idiot	Total	Per Cent
Familial defects	19	11	4	34	6.6
Undifferentiated defects	13	21	42	76	18.4
Cerebral palsy	6	5	21	32	32.3
Mongolism	..	2	..	2	2.2
Infection	6	5	10	21	41.2
Trauma	4	6	5	15	35.7
Craniofacial defects	..	..	5	5	15.2
Phenylpyruvic amentia	..	..	1	1	8.3
Cretinism	..	..	..	..	0
Cerebral lipoidosis	..	..	1	1	16.7
Muscular dystrophy	..	..	..	..	0
Congenital ectodermosis	..	1	2	3	60.0
Total	48	51	91	190	14.9

There were 12 patients with phenylpyruvic amentia. As previously noted,[2] most of these patients were classifiable in the idiot category although 1 was listed as a moron and 2 others as imbeciles, with intelligence quotients of about 45.

Cretinism was the only endocrine disorder found in this study to which mental defect could be causally related. Of the patients with muscular dystrophies, 4 had the pseudohypertrophic type; 1, the Landouzy-Dejerine type and 1 a condition diagnosed as amyotonia congenita. All of these patients except the one with amyotonia congenita were classified as morons. The finding of 6 patients with muscular dystrophy in the relatively small population making up the material of this study would suggest a possible relationship between the genetic factor responsible for the muscular disease and the mental defect.

The patients with mental defect which could be attributed with reasonable assurance to recurrent convulsions of unknown cause made up less than 4 per cent of the total. The mental classifications of these patients were almost entirely confined to the moron or high imbecile levels. It is apparent that idiopathic or hereditary epilepsy, which is responsible for the major proportion of convulsive disorders, was a relatively infrequent cause of mental deficiency in

2. Jervis, G. A.: The Genetics of Phenylpyruvic Oligophrenia, Proc. Am. A. Ment. Deficiency, 1939, p. 13.

is series. In addition to the 52 patients in is category, there were a total of 190 other atients with convulsive disorders, who were stributed throughout most of the other diagstic categories. The distribution of these paents is given in table 2. It will be noted that, nsidering only those groups in which the numers are large enough to warrant the drawing conclusions, the greatest incidence of assoated convulsive disorders occurred in those ersons with mental deficiency in whom either erebral trauma or cerebral infection was of iologic importance. Almost as important in is connection was the group with congenital erebral palsy. A third or more of the patients each of these three diagnostic categories sufered from recurrent convulsions. This observaon agrees with the fact that the greatest proortion of cases of the more severe grades of ental defect and presumably cerebral abnorality occurred in these three groups. As ight be expected, the incidence of associated nvulsive disorders seems to be directly related the severity of the mental defect. This relaion is readily illustrated in the table. Thus, e incidence of convulsive disorders in the oron classification is roughly 9 per cent, as mpared with 16 per cent in the imbecile group nd 21 per cent in the idiot classification. These ifferences are statistically significant. Among e morons whose defect was familial the incience of associated convulsive disorders was pproximately 4 per cent. The incidence of pilepsy in the general population is estimated t 0.5 per cent.[3] The presence of convulsions ncreases the likelihood of commitment to an nstitution of persons with mental deficiency of ll types, but this is especially true for those in he moron classification, since at the lower menal levels the severity of the mental defect of self is sufficient cause for institutionalization. t is, therefore, not unlikely that the incidence f convulsive disorders among morons whose ondition is familial is actually not much greater han would be found in the general population.

Approximately 30 per cent of the patients dmitted to institutions fail to exhibit signs or ymptoms which would allow classification in ny of the present categories. This undifferntiated group undoubtedly represents a wide ariety of etiologic factors, operative during arious periods of fetal life.

Although it is possible to place patients with reasonable degree of accuracy in the diagnostic categories of mongolism, cerebral palsy and craniofacial defects, it must be admitted that with regard to etiology one is not much better informed as to these groups than as to the undifferentiated group. Considering etiology alone, it is possible to classify the patients in three groups: namely, those with hereditary defects, those whose defects were acquired through infection or trauma and those, whether classifiable or not, for whom the cause of the defect is unknown. This classification has been made in table 3. The group with hereditary defects includes patients whose conditions fell into the following diagnostic categories: familial defects, phenylpyruvic amentia, idiopathic epilepsy, muscular dystrophy, cerebral lipoidosis and congenital ectodermosis. The group with defects of unknown cause includes those with mongolism, cerebral palsy, craniofacial defects, cretinism and undifferentiated conditions. It will be noted that almost 45 per cent of the patients admitted to the institution had cerebral abnormalities traceable to genetic factors. Only

TABLE 3.—*Classification of Diagnoses of Mental Defect as of Known or Unknown Origin*

	Moron	Imbecile	Idiot	Total	Per Cent
Hereditary	460	109	24	593	44.6
Acquired	17	28	48	93	7.0
Unknown	63	214	367	644	48.4
Total	540	351	439	1,330	100.0

7 per cent had abnormalities due to cerebral infections or trauma, while almost 50 per cent had defects due to factors at present unknown or only partially understood. Of greater importance is the fact that in the moron classification the hereditary factor was operative in 85 per cent of the cases. It is also of interest that as the severity of the mental defect became more pronounced the hereditary factor became less operative. Actually, in only 5 per cent of the idiot population could the defect be definitely attributed to genetic factors, while in 82 per cent the etiologic factors were unknown.

That the unknown factors responsible for cerebral abnormalities also play a role in producing anomalies elsewhere in the body is indicated in table 4. Because the incidence of noncerebral congenital malformations is known to be high in children with mongolism [4] and in those with cerebral palsy,[5] these two categories are listed

3. Penfield, W., and Erickson, T. C.: Epilepsy nd Cerebral Localization, Springfield, Ill., Charles C homas, Publisher, 1941, p. 310

4. Jervis, G. A.: Recent Progress in the Study of Mongolism, Am. J. Ment. Deficiency **46**:467, 1942.

5. Yannet, H.: The Etiology of Congenital Cerebral Palsy: A Statistical and Clinical Study, J. Pediat. **24**:38, 1944.

separately. The remaining categories, in which the etiologic factor is unknown, make up the third group. The incidence of noncerebral congenital defects in these groups is compared with that in the groups with hereditary and acquired defects, which are treated together. It will be noted that the total incidence of congenital defects is significantly greater in the patients with cerebral abnormalities of unknown cause, whether their defects are classifiable as mongolism or cerebral palsy or undifferentiated forms, than in the group with hereditary and acquired cerebral abnormality. The defects noted include, in addition to congenital cardiac involvement, cataracts, bilateral corneal opacities, microphthalmos, leukoma, clubfoot, webbing of fingers, spina bifida externa, harelip and cleft palate, bronchial cleft cyst, pseudohermaphroditism and megacolon. The most frequent defects are those of the heart, the eye and the skeleton. It will be noted that they were distributed somewhat differently among the group having defects of unknown cause. Thus, cardiac involvement occurred most frequently among the persons with mongolism, and especially those with hypertelorism, as previously indicated. Skeletal defects were more common among the patients with undifferentiated defects. Defects of the eye appeared most frequently among the patients with mongolism and cerebral palsy. Whether this peculiarity in association of certain types of congenital anomalies may have importance in relation to the problem of etiology must be determined by future studies. It is probable that since the organ systems differentiate at different periods of fetal life, these associations may give clues as to when the injurious factors may have become operative.

TABLE 4.—*Incidence of Noncerebral Congenital Malformations*

Malformation	Hereditary and Acquired Mental Defect	Classifiable and Undifferentiated Types of Mental Defect of Unknown Cause		
		Mongolism	Cerebral Palsy	Others
	(686)	(92)	(99)	(453)
Heart	5 (0.7%)	8 (8.8%)*	0	9 (2.0%)
Skeletal	0	2 (2.2%)	2 (2.0%)	15 (3.3%)*
Eye	2 (0.3%)	7 (7.6%)*	6 (6.1%)*	11 (2.4%)*
Face and neck	2 (0.3%)	0	1 (1%)	5 (1.1%)
Genitourinary	2 (0.3%)	2 (2.2%)	0	2 (0.4%)
Gastrointestinal	0	0	0	2 (0.4%)
Total	11 (1.6%)	19 (20.8%)*	9 (9.1%)*	44 (9.7%)*

* Statistically significant.

COMMENT

In evaluating the results of this analysis, it must be stressed that one is dealing with a somewhat selected sample of persons with mental deficiency, namely, patients requiring institutionalization. Random community studies of mental deficiency of a reasonably accurate nature are difficult to carry out, and there are few comparable investigations available. The survey in Great Britain, reported by the Woods Commission,[6] indicated that of the mentally defective persons in a selected community approximately 75 to 80 per cent were in the moron classification, as compared with the 40 per cent found by Penrose[7] in an institutional survey and the 44 per cent found in the present series. There is little doubt that from the point of view of magnitude and social import the moron represents the most significant aspect of the problem of mental deficiency. The importance of the observation that hereditary factors were considered responsible for the defect in almost 85 per cent of the patients in the moron classification is obvious. As the cerebral abnormality becomes more severe, the relative importance of heredity decreases. In the imbecile group only 31 per cent, and in the idiot group only 5.3 per cent, of the defects can be traced to this factor. It is also true that as the cerebral abnormality becomes more pronounced knowledge of the responsible etiologic factors decreases. Thus, in the moron group the mental defect was considered of unknown cause in less than 12 per cent, whereas the etiologic factor was unknown in 61 per cent of the imbecile group and in 84 per cent of the idiot group. That these unknown factors responsible for the cerebral abnormality are not necessarily specific for the central nervous system is indicated by the high incidence of noncerebral anomalies in the patients of this group (table 4). This association had previously been noted in cases of cerebral palsy[5] and mongolism,[4] but it holds equally true in the cases of so-called undifferentiated defects.

The patient with undifferentiated defects offers an unusual opportunity for the study of factors that may be injurious to the fetus. Recently preliminary evidence has been obtained that suggests the importance of maternal isoimmunization by the Rh factor in a small pro-

6. Report of the Mental Deficiency Commission. London, His Majesty's Stationery Office, 1929.

7. Penrose, L. S.: A Clinical and Genetic Study of 1280 Cases of Mental Defect, Medical Research Council, Special Report Series, no. 229, London, His Majesty's Stationery Office, 1938.

portion of these patients, roughly not over 5 to 10 per cent.[8] Similarly, maternal isoimmunization by the A and B blood factors has also been shown to be definitely a possible injurious mechanism.[9] The recent demonstration of the importance of rubella, and possibly other virus infections, in the mother[10] during the early weeks of pregnancy in producing ocular, and probably other, defects of developmental nature has opened an increasingly important field for consideration in relation to this problem. In addition, the work of Warkany[11] on the effect of maternal dietary deficiencies on the fetus is undoubtedly pertinent. Unfortunately, data relative to apparently minor infections and to the mother's diet when obtained many years after the birth of the child, as was the case with this series, are almost impossible to evaluate adequately. The need for specific diagnostic technics to aid in this phase of the problem requires no special stress.

While my data indicate the relatively minor place of the genetic factor in the etiology of the mental defect in idiots, this observation must be qualified, since it may not represent the complete picture. The presence of a recessive genetic factor in persons with mental defects can, as a rule, be recognized only from the occurrence of similar manifestations in siblings or, to a lesser extent, in other relatives. In the absence of pathognomonic physical or laboratory findings, such as exist, for example, for phenylpyruvic amentia or for the cerebral lipoidoses, diagnosis is dependent on the presence of a sufficiently large number of siblings to permit determination of the presence or absence of genetic recessivity. In only a relatively small proportion of this group were the families of sufficient size for one to be absolutely certain of the absence of a genetic factor. The possibility of mutations as the cause of sporadic idiocy must also be considered. The difficulties involved in evaluating this aspect of the problem have been discussed by Penrose.[12]

While the diagnosis of birth trauma can be made with a reasonable degree of reliability at the time of birth or within the following few months, this is not the case if the patient is seen for the first time later in life. At this time the diagnosis is extremely difficult. This is true because, with few exceptions, the neurologic phenomena appearing as late manifestations of birth trauma may be seen as well in cases in which the underlying pathologic condition in the brain is undoubtedly based on developmental abnormalities. Prenatal and natal cerebral inflammatory processes may also result in clinical pictures practically undistinguishable from those seen in proved cases of birth trauma. In a large percentage of cases it thus becomes necessary to rely almost entirely on the birth history for aid in establishing a diagnosis. Unfortunately for diagnosis, there is no type of delivery or obstetric complication at the time of delivery that is invariably, or even frequently, followed by cerebral injury. To complicate the picture further, even in cases in which a definite diagnosis of birth injury can be made after death, the birth history may not be considered definitely abnormal. Thus, Benda[13] found in 24 cases studied post mortem in which the pathologic findings were considered pathognomonic of birth trauma, 5 in which there was a history of "normal" birth, 2 in which there was a history of cesarian section and 2 in which delivery was with the aid of instruments but without additional evidence of unusual difficulty. In addition, evaluation of birth histories obtained some years afterward from mothers who have been exposed repeatedly to interim lay and medical opinions and suggestions is extremely difficult and frequently subject to error. It is thus apparent that the diagnostic classification of birth trauma in this series probably represents a minimal estimate and that a small but appreciable number of cases are included in the group with undifferentiated defects which may actually represent the end results of birth trauma.

SUMMARY AND CONCLUSIONS

In an analysis of the diagnostic classifications of 1,330 institutionalized patients with mental deficiency, it was possible to classify the defects of approximately 70 per cent, using easily recognizable diagnostic categories.

The hereditary factor was etiologically responsible for the mental defect in about 85 per cent

8. Yannet, H., and Liberman, R.: The Rh Factor in the Etiology of Mental Deficiency, Am. J. Ment. Deficiency **49**:133, 1944.

9. Polayes, S. H.: Erythroblastosis Fetalis in Mothers with Rh-Positive Blood: Report of Six Cases, with Comment on Isoimmunization with the "A" and "B" Agglutinogens, Am. J. Dis. Child. **69**: 99 (Feb.) 1945. Yannet, H., and Lieberman, R.: The "A" and "B" Agglutinogens in the Etiology of Congenital Cerebral Abnormalities, to be published.

10. Erickson, C. A.: Rubella Early in Pregnancy Causing Congenital Malformations of Eyes and Heart, J. Pediat. **25**:281, 1944.

11. Warkany, J.: Congenital Malformations Induced by Maternal Nutritional Deficiency, J. Pediat. **25**:476, 1944.

12. Penrose, L. S.: Autosomal Mutation and Modification in Man with Special Reference to Mental Defect, Ann. Eugenics **7**:1, 1936.

13. Benda, C. E.: The Late Effects of Cerebral Birth Injuries, Medicine **24**:71, 1945.

of the morons, 31 per cent of the imbeciles and 5 per cent of the idiots.

Recurrent convulsions (idiopathic or hereditary epilepsy) were considered responsible for the mental defect in less than 4 per cent of the patients.

The incidence of associated convulsive disorders was directly related to the severity of the mental defect occurring in 21 per cent of the idiots, in 16 per cent of the imbeciles and in 9 per cent of the morons. In the groups with post-traumatic and postinfectious defects a cerebral palsy, the incidence of convulsive d orders was approximately 30 per cent.

The high incidence of noncerebral develo mental anomalies associated with certain of t categories of mental deficiency as compared wi the incidence with the acquired or hereditar forms suggests nonspecificity for some of t etiologic factors now unknown, or poorly unde stood.

Southbury Training School.

STUDIES ON THE CONTROL OF ACUTE INFECTIONS OF THE RESPIRATORY TRACT

IV. CONTINUOUS ORAL ADMINISTRATION OF SULFADIAZINE TO CHILDREN HIGHLY SUSCEPTIBLE TO INFECTION

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In the course of studies on the oral use of sulfadiazine against bacterial complications of illnesses of the respiratory tract,[1] data were obtained on some of the limitations of continuous administration of sulfonamide compounds.[2] Although there were no serious toxic effects, prolonged use of the drug led to the dissemination of drug-resistant bacteria [3] and had little demonstrable prophylactic value under the conditions prevailing during the study.[2a] The negative clinical findings were not unexpected because of the highly selective bacteriostatic action of sulfonamide compounds. In time, additional clinical data on the continuous application of sulfadiazine became available in connection with various phases of the problem. Since all the clinical data obtained were comparable, they have been collected and are presented at this time because of the renewed interest in chemoprophylaxis following numerous reports on its value to persons exposed to infections of the respiratory tract [4] or susceptible to their after-effects.[5]

From the Division of Infectious Diseases, the Public Health Research Institute of the City of New York, Inc.

Aided by a grant from the Metropolitan Life Insurance Company on the recommendation of the Influenza-Pneumonia Commission.

The sulfadiazine employed was supplied by Lederle Laboratories, Inc., Pearl River, N. Y.

The physicians at Letchworth Village, Thiells, N. Y., particularly Dr. Harry C. Storrs, Superintendent, cooperated in the work.

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2. (*a*) Siegel, M., and Julianelle, L. A.: The Epidemiology of Acute Respiratory Infections Conditioned by Sulfonamides: I. General Clinical Considerations, Ann. Int. Med. **22**:1-9 (Jan.) 1945. (*b*) Julianelle, L. A., and Siegel, M.: The Epidemiology of Acute Respiratory Infections Conditioned by Sulfonamides: II. Gross Alterations in the Nasopharyngeal Flora Associated with Treatment, ibid. **22**:10-20 (Jan.) 1945; (*c*) III. Effects of Treatment on the Organism and Carrier of Diphtheria, ibid. **22**:21-28 (Jan.) 1945; (*d*) IV. Trends in Pneumococcal Types Initiated by Drug Treatment, ibid. **22**:29-39 (Jan.) 1945.

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(Footnote continued on next page)

PLAN OF STUDY

The subjects observed were physically normal, feeble-minded boys and girls, who were segregated in two cottages at Letchworth Village (cottages Y and Iota). They lived in overcrowded quarters, about 140 children to a cottage. Selected samples of these populations were chosen for the study in various ways, depending on the objective of the particular problem.[6] Sulfadiazine was given orally to three sets of children: viz., (*a*) alternate new patients admitted between August 1942 and April 1943, (*b*) half of the children living in a single dormitory in cottage Iota[2a] and (*c*) half of a group of carriers of beta hemolytic streptococci living in cottage Y. The untreated half in each unit served as controls.

In all, 128 children were observed; 64 in the treated group and 64 in the control group. They varied in age from 2 to 14 years and in weight from 22 pounds (10 Kg.) to 88 pounds (40 Kg.). For each treated group there was a comparable control group living under similar conditions and managed alike except that they received no sulfadiazine. The children in the treated group received from 0.5 to 2 Gm. of sulfadiazine daily for periods ranging from one month to fifteen weeks, between August 1942 and April 1944. During these twenty months the drug was applied for a total of one hundred and sixty-two person months of treatment, of which 94 per cent occurred between December and April, when the incidence of severe acute infections of the respiratory tract is usually high. Whenever illnesses of the respiratory tract occurred in the treated group, the patients in this group regularly received at least 2 Gm. of sulfadiazine daily for four days and 1 Gm. daily for an additional three days, while those in the control group remained untreated.

RESULTS

The epidemiologic conditions prevailing at the institution during the therapeutic period were unusual, particularly for the susceptible groups under observation. There were no outbreaks of severe illnesses of the respiratory tract, such as had occurred in past years. The infections observed were consistently mild and free from complications in most instances. This fact was reflected in the small number of patients with pneumonia admitted to the hospital. In fact, the incidence of pneumonia was the lowest ever experienced in cottages Y and Iota (table 1). Only 1 case of pneumonia was observed in cottage Y between December 1942 and April 1943, instead of the 3 to 8 cases expected from past experiences, and 3 were observed in cottage Iota, instead of the expected 7 to 19. Contrary to expectations, therefore, the exposure to an incidence of severe bacterial infections were unusually low at the time the drug was used prophylactically. The effects of the prevailing conditions on the results obtained in the study will be brought out later in the paper.

The number of acute illnesses of the respiratory tract observed in each test group during the therapeutic period and the first two months

TABLE 1.—*Number of Patients with Pneumonia in Cottages Y and Iota During Past Five Years**

Month	1939-1940 Y	1939-1940 Iota	1940-1941 Y	1940-1941 Iota	1941-1942 Y	1941-1942 Iota	1942-1943 Y	1942-1943 Iota	1943-194 Y	1943-194 Iota
July	1	1	0	1	3	2	0	0	1	1
August	0	3	0	1	3	1	0	0	0	0
September	0	7	1	0	0	2	0	1	0	1
October	0	7	2	0	0	3	0	0	1	0
November	0	3	0	0	0	1	0	0	0	1
December	1	2	1	0	1	1	0	0	1	3
January	4	3	0	1	4	4	0	1	0	4
February	1	8	0	0	0	0	1	1	0	2
March	1	3	1	7	1	3	0	0	1	0
April	2	5	2	9	1	0	0	1	0	1
May	8	3	3	3	0	1	0	4	0	2
June	2	0	2	6	0	3	0	3	0	0
Total	20	45	12	28	13	21	1	11	4	15
Rate per 1,000	15.4	34.6	9.2	21.5	10.0	16.2	0.7	7.9	2.8	10.7

* Enclosed area represents therapeutic periods in the two cottages.

after interruption of continuous therapy is given in table 2. During the therapeutic period the incidence of acute illnesses was remarkably alike in almost all tests for treated and for control groups. After cessation of continuous therapy, the children in the treated group were somewhat more frequently affected than those in the control group, but the difference was not considered significant for the limited experience.

With few exceptions the illness during the therapeutic period was mild, uncomplicated acute nasopharyngitis, occasionally associated with tonsillitis or tracheobronchitis. There were single cases of scarlet fever, pulmonary abscess and lobar pneumonia, of undetermined cause, all in the control group. After the therapeutic period, in addition to the usual cases of nasopharyngitis with or without bronchitis, there were 3 cases

53 (Jan.) 1943. (*i*) Kuttner, A. G., and Reyersbach, G.: The Prevention of Streptococcal Upper Respiratory Infections and Rheumatic Recurrences in Rheumatic Children by the Prophylactic Use of Sulfanilamide, J. Clin. Investigation **22**:77-85 (Jan.) 1943. (*j*) Messeloff, C. R., and Robbins, M. H.: The Prophylactic Use of Sulfanilamide in Children with Rheumatic Heart Disease, J. Lab. & Clin. Med. **28**:1323-1327 (Aug.) 1943. (*k*) Feldt, R. H.: Sulfanilamide as a Prophylactic Measure in Recurrent Rheumatic Infection: A Controlled Study Involving 131 "Patient-Seasons," Am. J. M. Sc. **207**:483-488 (April) 1944. (*l*) Dodge, K. G.; Baldwin, J. S., and Weber, M. W.: The Prophylactic Use of Sulfanilamide in Children with Inactive Rheumatic Fever, J. Pediat. **24**:483-501 (May) 1944. (*m*) Holbrook, W. P.: The Army Air Forces Rheumatic Fever Control Program, J. A. M. A. **126**:84-87 (Sept. 9) 1944. (*n*) Thomas, C. B.: The Prevention of Recurrences in Rheumatic Subjects, ibid. **126**:490-493 (Oct. 21) 1944.

6. Siegel.[1a] Siegel and Julianelle.[2a]

pneumonia, 2 in the treated group and 1 among the controls, and 9 cases of scarlet fever, 4 in the treated group and 4 among the controls. An affected child in each test group died during the post-therapeutic period following an attack of scarlet fever complicated by bronchopneumonia. Thus, the number and nature of the illnesses observed during and after continuous therapy were comparable in the two test groups with the exceptions noted among the controls during the therapeutic period.

Although the incidence of acute infections of the respiratory tract was not demonstrably altered by the prophylactic doses of sulfonamide compounds used, the course of the illnesses observed appeared to be modified somewhat. The acute

TABLE 2.—*Number of Patients with Acute Febrile Infections of Respiratory Tract During Period of Continuous Therapy and During First Two Months After Cessation of Continuous Therapy*

			Illnesses			
			Therapeutic Period		Post-therapeutic Period	
Unit	Group	Number of Subjects	Children Affected	Attacks	Children Affected	Attacks
I*	Treated	23	4	5	8	10
	Controls	23	4	5	9	11
II†	Treated	30	7	8	6	9
	Controls	30	7	8	5	5
III‡	Treated	11	3	3	1	1
	Controls	11	4	4	1	1
Totals	Treated	64	14	16	15	20
	Controls	64	15	17	15	17
	Total	128	29	33	30	37
Rate, per cent	Treated		21.9	25.0	23.4	31.3
	Controls		23.1	26.6	23.4	26.6
	Total		22.7	25.8	23.4	28.9

* New entrants to cottages Y and Iota between August 1942 and April 1943. Treated subjects received 0.5 to 0.75 Gm. of sulfadiazine daily for one to three months from date of admission.

† Population of one dormitory in cottage Iota. Treated subjects received 1 to 2 Gm. of sulfadiazine daily for fifteen consecutive weeks, from Dec. 11, 1942 to March 25, 1943.[2a]

‡ Carriers of hemolytic streptococci in cottage Y. Treated subjects received 1 Gm. of sulfadiazine daily for twelve weeks, between Jan. 14 and April 14, 1944.

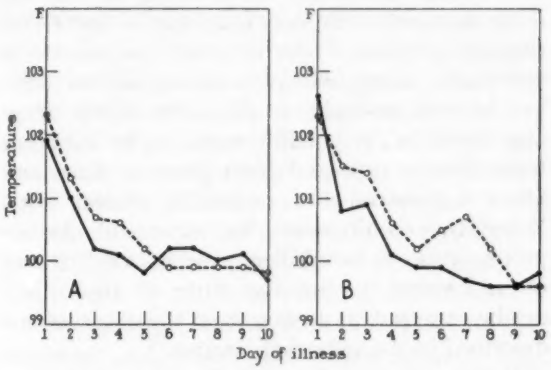
febrile stage for the treated patients tended to be shortened and to be less affected by spontaneous fluctuations in severity than that for the untreated patients (chart).

The concentration of free sulfadiazine in the blood maintained during the study varied considerably with the individual patient. With a daily maintenance dose of 1 Gm. the level of free sulfadiazine in the blood varied from 1.7 to 8.1 mg., the average being 3.5 mg. per hundred cubic centimeters. When the dose was doubled, the blood level ranged from 3.2 to 13.9 mg., with a mean of 7.2 mg. per hundred cubic centimeters.

There were no serious toxic effects. The well-being of the treated children was not apparently impaired by prolonged or repeated use of sulfadiazine. A transient rash was encountered in 2 children, and many had microscopic red blood cells in the urine during the period of therapy. The average gain in weight was slightly higher among the treated children than among the controls, by an amount which was not statistically significant.

COMMENT

In the clinical experience just described, the incidence of acute illnesses of the respiratory tract was almost the same for children under continuous sulfonamide therapy as for comparable controls. While most of the patients in both test groups were mildly sick and improved promptly without complications, the few who did not improve rapidly were predominantly, but not



Average daily maximum temperature for patients treated with sulfadiazine and for untreated (control) patients with acute illnesses of the respiratory tract (*A*) during the period of continuous therapy and (*B*) after cessation of continuous therapy.

In this chart, the solid line with circles represents values for treated patients; the broken line with hollow circles, values for untreated patients.

The curves in *A* represent values for 16 treated patients and for 17 untreated patients; those in *B*, values for 20 treated patients and 17 untreated patients.

exclusively, in the control group. Although the drug appeared to have a therapeutic effect in some cases which followed the general pattern described in previous reports,[1] its prophylactic value in the dose used was not demonstrable under the prevailing conditions.

These findings differ from those reported for the military forces, in which a sharp decline in acute infections of the respiratory tract was noted after the prophylactic use of sulfadiazine.[4a, b] In the current study, there was also a sharp decline in the incidence of pneumonia and other severe bacterial infections requiring hospitalization of the patient during the period of continuous therapy. However, the decline in morbidity was seen not only among the treated patients but

among the controls, and its relationship to sulfonamide therapy was probably coincidental.

It is noteworthy that the decrease in complicating bacterial infections should have occurred at a time when a rise was anticipated because of unfavorable conditions arising during the war, from increasing overcrowding and inadequate personnel. Without the use of satisfactory controls the changes observed might have been attributed solely to the use of sulfadiazine, as indeed they were by some of the physicians at the institution before they had seen the data on the control group.

The failure to demonstrate the prophylactic efficacy of continuous sulfonamide therapy does not necessarily detract from the usefulness of the procedure in proper circumstances but reveals some of its limitations and emphasizes the need for suitable conditions if favorable results are to be obtained. The demonstration of successful chemoprophylaxis requires the existence of specifically susceptible persons exposed to virulent bacteria amenable to the action of the drug. Variations in the conditions are to be expected from time to time and from place to place and affect the outcome of controlled clinical tests. When the requirements for successful chemoprophylaxis can be fulfilled, excellent results may be anticipated [7]; otherwise little, if any, effect can be expected, as is seen from the observations described in the preceding section.

From a practical standpoint, therefore, one must either carefully select an appropriate group and period for application of chemoprophylaxis, as was done for the military forces,[4] or use the drug continuously, as has been advocated for the treatment of rheumatic fever.[5] The former method may involve the mass use of the drug for all exposed persons and bears the responsibility of causing severe reactions, even though their incidence is low.[4e] The latter method may involve the use of the drug for a period of months or years [5n] and increases the possibili of producing drug-resistant strains,[2] which m readily increase the incidence of the disease epidemic proportions.[3a]

7. Footnotes 4 and 5.

SUMMARY AND CONCLUSION

The clinical effects of continuous oral admi istration of sulfadiazine on the incidence a severity of acute infections of the respirato tract were observed in 128 physically norm children, half of whom were treated and h untreated.

The drug was used between August 1942 a April 1944 for periods of four to fifteen consec tive weeks in doses ranging from 0.5 to 2 G daily. The average level of free sulfadiazine the blood was 3.5 mg. per hundred cubic cent meters with a maintenance dose of 1 Gm. a d and 7.2 mg. per hundred cubic centimeters wi 2 Gm. a day. In no case was the use of the dru discontinued because of serious toxic reaction

The incidence of acute infections of the respir tory tract was almost the same for treated a for control children. However, the treate patients, as a group, recovered somewhat mo promptly than the controls and experienced few complicated illnesses and fluctuations in severit Since the illnesses observed were unexpected few and were milder than anticipated, the ant biotic effects of sulfadiazine were not readi demonstrable.

While the prophylactic use of sulfonamid compounds is of recognized value in certain ci cumstances, their usefulness is limited by factor pertaining to the host and the infecting agent which might not be accurately predictable. If, con trary to expectations, the prevailing condition are not suitable for successful chemoprophylaxis the drug may be employed for prolonged period with relatively little, if any, additional advantage over prompt therapeutic application and not with out some danger to the individual and th community.

STUDIES ON THE STREPTOCOCCI ("ENTEROCOCCI") OF LANCEFIELD GROUP D

I. SEROLOGIC AND BIOCHEMICAL CHARACTERISTICS

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In the course of carrier studies on infants and cultures isolated from infected persons in the same age group, a large number of strains classified as group D (Lancefield) were encountered. The frequency with which these strains were encountered, together with the relative scarcity of work done on this serologic group as compared with that on the Lancefield group A (in which the majority of organisms causing human infections are placed) seemed to justify analysis. The present interest in group D was further stimulated by the isolation of a strain of streptococci, originally misclassified as group E in another laboratory, from an infant with an acute, fulminating infection. It was not until rabbits had been immunized with this strain and reciprocal absorption tests had been done with the resulting serum and with known strains of the various serologic groups that the correct identity of this strain was established. The possible significance of group D in human infections will be discussed in part II of this study.

SEROLOGIC CLASSIFICATION

The older literature on the "enterococci" has been reviewed by Sherman.[1] It might be mentioned here that Durand and Dufour,[2] Meyer and Löwenstein[3] and Grumbach and Schnetz[4] described four serologic types of "enterococci." Streptococci of group D were first described by Lancefield.[5] The original strains were isolated from cheese and proved later to be identical with strains classified as Streptococcus zymogenes by biochemical methods.[6] Subsequent work placed several additional strains, previously classified as "enterococci" by cultural and biochemical characteristics, in group D on the basis of specific precipitation of the extracted group substance with serums of rabbits immunized with known group D organisms. Hare and Maxted[7] and Lancefield and Hare[8] reported that most "enterococci" belonged to group D. Sherman[6] found the strains identified as Streptococcus liquefaciens and Streptococcus durans to belong to group D. Thus, many of the metabolic gradients in a single species, as differentiated on the basis of biochemical and physiologic characteristics, have been identified as containing a common antigen.

The existence of serologic types within group D has been mentioned by Lancefield.[9] Houston,[10]

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1. Sherman, J. M.: The Streptococci, Bact. Rev. 1:1, 1937.

2. Durand, P., and Dufour, P.: La groupe de l'enterocoques—ses caractères cultureaux—sa place dans la classification, Arch. Inst. Pasteur de Tunis **12**:229, 1923.

3. (*a*) Meyer, K.: Ueber spezifische Agglutination der Enterokokken, Centralbl. f. Bakt. (Abt. 1) **99**:146, 1926. (*b*) Meyer, K., and Löwenstein, H.: Ueber spezifische Agglutination der Enterokokken, Ztschr. f. Immunitätsforsch. u. exper. Therap. **47**:39, 1926.

4. Grumbach, A., and Schnetz, A.: Serologische Enterokokken-Differenzierung, Schweiz. Ztschr. f. allg. Path. u. Bakt. **1**:59, 1938.

5. Lancefield, R. C.: A Serological Differentiation of Human and Other Groups of Hemolytic Streptococci, J. Exper. Med. **57**:571, 1933.

6. Sherman, J. M.: The Enterococci and Related Streptococci, J. Bact. **35**:81, 1938.

7. Hare, R., and Maxted, W. R.: The Classification of Hemolytic Streptococci from the Stools of Normal Pregnant Women and Cases of Scarlet Fever by Means of Precipitation and Biochemical Tests, J. Path. & Bact. **41**:313, 1935.

8. Lancefield, R. C., and Hare, R.: The Serological Classification of Pathogenic and Non-Pathogenic Strains of Hemolytic Streptococci from Parturient Women, J. Exper. Med. **61**:335, 1935.

9. Lancefield, R. C.: Unpublished data; cited by Sherman.[1]

10. Houston, T.: Enterococci, Proc. Internat. Cong. Microbiol. **2**:141, 1936.

Graham and Bartley [11] and Sylvester and Benedict [12] reported the existence of distinct serologic types in group D. In this laboratory, serums for four serologic types have been developed, Lancefield's original group D strains being used as antigens. The serums used here for the classification of an unknown strain included Lancefield's groups A through M. When an extract of an unknown strain was precipitated with group D serum, it was then retested with type-specific serums prepared against strains H 69D5, Lanc 1, Lanc 3 and D 76 [13] (types 1, 2, 3 and 4 respectively).

Methods.—Crude hydrochloric acid extracts containing C and M substances were prepared and tested according to the method described by Lancefield.[14] Purified C and M fractions of this crude extract were prepared according to the method described by Hirst and Lancefield.[15] The growth in 500 cc. of broth was extracted in 20 cc. of twentieth-normal hydrochloric acid and neutralized to p_H 7.0 with normal sodium hydroxide solution. Four volumes of 95 per cent alcohol was added and the extract stored in the refrigerator (— 6 C.) for twenty-four hours. The precipitate was collected and redissolved in 10 cc. of isotonic solution of sodium chloride and reprecipitated with 3 volumes of 95 per cent alcohol in the refrigerator for twenty-four hours. This precipitate, containing the M substance, was collected, dried in a stream of compressed air, redissolved in 5 cc. of isotonic solution of sodium chloride and centrifuged clear of insoluble material. The alcoholic supernatants of the two precipitations, containing the C substance, were combined and evaporated to dryness in a water bath held at 56 to 58 C., redissolved in 5 cc. of distilled water and centrifuged clear of insoluble material.

Fractions so prepared were tested with Molisch, Millon, biuret and xanthoproteic reagents. If the fractions were grossly impure, the alcoholic precipitations were repeated and the precipitates and supernatants collected and redissolved as before.

One cubic centimeter samples of purified fractions C and M were digested with 0.5 cc. of 5 per cent trypsin at 37 C. for twenty-four hours. After such digestion, the samples were acidified with normal hydrochloric acid, heated to 60 C. for one-half hour, neutralized to p_H 7.0 with normal sodium hydroxide solution and recentrifuged if necessary. As a control on the dilution of the serum by the addition of trypsin, similar samples with 0.75 cc. of isotonic solution of sodium chloride were tested with the digested samples.

The type and group serums used in this study were prepared by the injection of formaldehyde-treated vaccines prepared from young, actively growing sixteen hour cultures. Rabbits weighing 2 to 3 Kg. were given injections of 1 cc. doses on three successive days, rested three days, then trial bled and tested. Rabbits varied in response to the antigens, usually taking at least two such courses of immunization before antibodies were observed by means of precipitin tests. For certain animals if additional immunization was indicated, the dose was increased to 2 cc. For others, small doses of living culture were given after one or two courses of formaldehyde-treated vaccine. Type antibodies appeared first in all animals and were easily lost by overimmunization unless the antibody titer was checked frequently and the animal bled before the serum became group specific (or nonspecific). Immunization with relatively small doses administered over a relatively long period (for the amount of antigen) was more successful than large doses. In general, type-specific antiserums of high titer were more easily produced than a good group-specific serum of corresponding titer. When sufficient titer was obtained (4 + in a 1 : 100 dilution or better) the animals were exsanguinated from the carotid artery with strict asepsis and the serum was collected and tested for specificity against extracts of all known serologic groups (groups A through M) and absorbed with dried whole cultures of homologous and heterologous types of group D strains.

TABLE 1.—*Results of Reciprocal Absorption Tests Showing Antigenic Relationship of Serologic Types in Group D (Lancefield)*

Serum	Absorbed with Culture *	Tested with Extract of
H 69 D5 (type 1)	H 69 D5 (type 1)	H 69 D5 (type 1) —
	Lanc 1 (type 2)	+
	Lanc 3 (type 3)	+
	D76 (type 4)	±†
Lanc 1 (type 2)		Lanc 1 (type 2)
	H 69 D5	+
	Lanc 1	—
	Lanc 3	+
	D76	+
Lanc 3 (type 3)		Lanc 3 (type 3)
	H 69 D5	+
	Lanc 1	+
	Lanc 3	—
	D76	+
D76 (type 4)		D 76 (type 4)
	H 69 D5	±†
	Lanc 1	+
	Lanc 3	+
	D76	—

* Serums absorbed with one-half volume of dried whole cells in shaking machine for periods varying from two to eight hours. Absorption of different type antibodies done separately on samples of same rabbit bleeding.

† Slight reduction in titer.

TABLE 2.—*Precipitation Tests with Crude Hydrochloric Acid Extracts of Group D (Lancefield) Streptococci and Group-Specific and Type-Specific Serums*

Serologic Type	No. of Cultures	Lancefield Group Serums A—M (Except D)	Group D	Serums for Types in Group D: H 69 D5 (T1)	Lanc 1 (T2)	Lanc 3 (T3)	D76 (T4)
H 69 D5 (type 1).....	100	—	+	+	—	—	±
Lanc 1 (type 2).....	31	—	+	—	+	—	—
Lanc 3 (type 3).....	3	—	+	—	—	+	—
D76 (type 4).....	2	—	±	—	—	—	+

Table 1 indicates the antigenic relationship of the serologic types in group D as determined

11. Graham, N. C., and Bartley, E. O.: Some Observations on the Classification of the Enterococci, J. Hyg. **39**:538, 1939.

12. Sylvester, J. C., and Benedict, R. G.: Some Observations on the Physiological and Serological Characteristics of Enterococci, J. Bact. **42**:138, 1941.

13. Dr. R. C. Lancefield, Rockefeller Institute, New York, supplied these strains as well as samples of group D serums for comparative tests.

14. Lancefield, R. C.: The Antigenic Complex of Streptococcus Hemolyticus, J. Exper. Med. **47**:91, 1928.

15. Hirst, G. K., and Lancefield, R. C.: Antigenic Properties of the Type-Specific Substance Derived from Group A Streptococci, J. Exper. Med. **69**:425, 1939.

reciprocal absorption tests. Table 2 summarizes the classification of one hundred and

TABLE 3.—*Precipitation Tests with Purified C and M Fractions Extracted from Group D (Lancefield) Streptococci*

Serologic Type	Extract	Group D Serums	Serums for Types in Group D: H 69 D5 (T1)	Lanc 1 (T2)	Lanc 3 (T3)	D76 (T4)
69 D5 (T1)	Crude extract,	+	+	—	—	±*
ne 1 (T2)	contains both	+	—	+	—	—
ne 3 (T3)	C and M	+	—	—	+	—
(T4)		+	±	—	—	+
69 D5	Purified C †	—	+	—	—	±
ne 1		+	—	—	—	—
ne 3		—	—	—	+	—
		—	±	—	—	+
69 D5	Purified M ‡	+	±	±	±	±
ne 1		—	—	+	—	—
ne 3		+	±	±	±	±
		+	±	±	±	±

* Denotes fine, granular precipitate after overnight incubation refrigerator; no ring reaction in incubator.
† Tryptic digestion did not affect serologic activity.
‡ Tryptic digestion destroyed serologic activity.

irty-six strains of group D streptococci with ur type-specific antiserums. The results of pre-

to differentiate the types within group B and by Simmons and Keogh [18] for the differentiation of types among group C strains, slide agglutination was attempted with the type-specific serums de-

TABLE 4.—*Chemical Characteristics of Purified C and M Substances Extracted from Group D (Lancefield) Streptococci*

Culture	Fraction	Chemical Tests: Molisch	Biuret	Millon's	Xanthoproteic
H 69 D5 (T1)					
Lanc 1 (T2)	Crude extract *	+	—	+	+
Lanc 3 (T3)	Purified C *	+	—	—	—
D76 (T4)	Purified M *	—	—	+	+

* All types.

veloped for group D. Table 5 summarizes the results of such tests with group D streptococci and various strains of other groups and types used as controls. Granularity and autoagglutination

TABLE 5.—*Comparison of Precipitation and Slide Agglutination Tests on Group D (Lancefield) Streptococci with Group and Type Serums*

Serologic Type	Number of Cultures	Griffith Serum (Group A) Types 1-30, Agg.	Lancefield Group Serums A—M (Except D) Agg.	Ppct.	Group D Serums Agg.	Ppct.	Serums for Types in Group D: H 69 D5 (T1) Agg.	Ppct.	Lanc 1 (T2) Agg.	Ppct.	Lanc 3 (T3) Agg.	Ppct.	D76 (T4) Agg.	Ppct.
69 D5 (type 1).....	100	—	—	—	+	+	+	+	—	—	—	—	±	±
anc 1 (type 2).....	31	—	—	—	+	+	—	—	+	+	—	—	—	—
anc 3 (type 3).....	3	—	—	—	+	+	—	—	—	—	+	+	—	—
76 (type 4).....	2	—	—	—	+	+	±	±	—	—	—	—	+	+
ontrols:														
Lancefield group strains A — M (except D).....	15	+ *	Not done	+ †	—	—	—	—	—	—	—	—	—	—
riffith types 1-30.....	27	+ *	Not done	+ ‡	—	—	—	—	—	—	—	—	—	—

* Group A strains with specific type only.
† Specific for group.
‡ In group A serums only.

pitation tests with the M protein-like substance nd the C carbohydrate extracted from these rains are summarized in table 3. Results of ertain tests as to the chemical nature of the xtracted substances are summarized in table 4.

It appears from these observations that the roup specific substances of types 1, 3 and 4 are robably protein, while type specificity is deter-ined by the carbohydrate substances. Type 2 distinct from the other types in that the type ubstance seems to be a protein. These observa-ons present partial confirmation of the work of ouston,[10] who reported the production of two erologically distinct "soluble substances" by ifferent strains of streptococci of group D, a hird strain failing to produce "soluble sub-tance."

Since Griffith's method [16] of slide agglutina-on was applied successfully by Stablefourth [17] presented no problem, since diffuse nongranular growth in broth cultures appears to be characteristic of group D organisms.

REACTION ON BLOOD AGAR

The discovery of streptococcus hemolysins [19] and the introduction of blood agar [20] led to the

16. Griffith, F. F.: The Serological Classification of Streptococcus Pyogenes, J. Hyg. **34**:542, 1935.

17. Stablefourth, A. W.: Serological Types of Streptococcus Agalactiae (Group B) in This and Other Countries, J. Path. & Bact. **45**:263, 1937.

18. Simmons, R. T., and Keogh, E. V.: Physiological Characters and Serological Types of Hemolytic Streptococci of Groups B, C and G from Human Sources, Australian J. Exper. Med. & Biol. Sc. **18**:151, 1940.

19. Marmorek, A.: L'unité des streptocoques pathogènes pour l'homme, Ann. Inst. Pasteur **16**:137, 1902.

20. Brown, J. H.: The Use of Blood Agar for the Study of Streptococci, Monograph 9, Rockefeller Institute for Medical Research, 1919.

almost universal belief that streptococci could be assigned to categories of differing diagnostic significance depending on the production of alpha, beta or gamma reactions on blood agar. Later work has indicated that hemolytic activity as assayed on blood agar is not a constant characteristic, even within the same serologic group. Stablefourth [21] and Lancefield [22] reported nonhemolytic variants in group B. Edwards [23] reported alpha variants of group C strain. Nonhemolytic strains are encountered frequently in groups H and K but rarely in group A,[24] although Fry [25] reported the production of alpha variants by a strain of group A streptococci. The loss of hemolytic activity by a group A strain also has been observed in this laboratory. Group D strains vary in their reaction on blood agar.[24] to beta also were observed. Similar observations have been recorded by Meyer.[3a]

The tube hemolysis test [26] was used as a supplement to standard blood agar in the study of the strains reported here.

Methods.—Huntoon's [27] unenriched hormone agar with 5 per cent sterile defibrinated horse blood was used. Formulas were constant, and each lot of agar was tested with known alpha and beta strains of streptococci before use. Young broth cultures were streaked on blood agar and incubated at 37 C. for twenty-four and forty-eight hours. Partial or complete anaerobiasis showed no qualitative differences in reaction.

The tube tests for soluble hemolysin were done with fresh, defibrinated and washed rabbit erythrocytes in a 5 per cent suspension in normal isotonic solution of sodium chloride. Although hemolytic activity varies with the species of cell used, rabbit erythrocytes were selected as being the most sensitive readily available indicator. Five tenths cubic centimeters of a ten to sixteen hour broth

TABLE 6.—*Biochemical Characteristics of Streptococci of Group D (Lancefield)*

Serologic Type	Number Strains	Reaction on Blood Agar	Production of: Soluble Hemolysin	Production of: Erythrogenic Toxin	Production of: Mouse Virulence	Heat Resistance	Reduced Methylene Blue	Hydrolyzed Sodium Hippurate	Fermented: Trehalose	Fermented: Sorbitol	Fermented: Lactose	Fermented: Mannitol	Fermented: Salicin	Range of Final
			Per Cent of Strains											
H 69 D5 (type 1)	100	Alpha 27 Beta 71 Gamma 2	0	0	3*	5	100	0	100	91	97	77	94	4.2–4
Lane 1 (type 2)	31	Alpha 48 Beta 43 Gamma 9	0	0	0	22	100	0	100	100	100	64	100	4.2–4
Lane 3 (type 3)	3	Alpha 66 Beta 33 Gamma	0	0	0	0	100	0	100	100	100	33	100	4.4–4
D76 (type 4)	2	Alpha Beta 100 Gamma	0	0	0	100	100	0	100	100	100	100	100	4.4–4
Total, all types	136	Alpha 34 Beta 62 Gamma 4	0	0	2	10	100	0	100	93	98	73	95	4.2–4

* M.L.D. = 0.25 cc. of eighteen hour broth culture.

In the present study the instability of blood agar reactions in this group has been observed repeatedly in stored strains; cultures showing beta reactions on primary isolation frequently were found to show alpha reactions after storage. Reverse changes, from alpha to beta or gamma

culture in streptococcus toxin broth [28] was combined with 0.5 cc. of 5 per cent suspension of rabbit erythrocytes and incubated in a water bath at 37 C. for two hours, centrifuged and examined for evidence of hemolysis. Cells in isotonic solution of sodium chloride and tests with known positive and negative strains (Lancefield J 17 A4 and O 90R, respectively) were included as controls.

The results of these tests are recorded in table 6. Alpha, beta and gamma strains were encountered in group D, with no correlation between blood agar reaction

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d serologic type. None of the strains tested produced uble hemolysin (table 6).

BIOCHEMICAL TESTS

Houston and McCloy[29] described the "enrococci" as being heat resistant. Heat-resistant rains, as well as those growing only at high mperatures,[30] have been shown to belong to oup D.[1]

Methods.—All strains were tested for the ability to thstand 62.8 C. for one-half hour, the criterion used Sherman.[6] One cubic centimeter samples of young, ive cultures were heated in a water bath at a temrature of 62 to 63 C. in an equal volume of sterile oth for one-half hour, the cultures allowed to cool, en streaked on a 5 per cent horse blood agar and cubated at 37 C. for forty-eight hours.

As is shown in table 6, relatively few (10 per nt) of the strains tested were resistant to heat. he ability to withstand high temperature could t be correlated with serologic type. Neither uld it be correlated with the inability to ferment annitol, as observed by Houston and McCloy.[29] seems reasonable to suspect the validity of e heat test, commonly used as a criterion for e differentiation of the "enterococci" from her streptococci.

Fermentation Reactions.—The carbohydrates used in is study were in 1 per cent solution in dextrose-free oth with 3 per cent chlorophenol red.[31] The methylene ue was used in a 1 per cent (final) dilution in sterile im milk, being added to final concentration in the rm of 1.6 per cent alcoholic solution.[32] All carbodrates and other mediums used in these tests were oculated with 0.1 cc. of an eighteen hour broth culre and observed after one, two, seven and fourteen ys' incubation at 37 C. The results are recorded in ble 6.

Final p_H.—This was determined by the methods deribed by Ayers[33] and Avery.[34] Beef infusion broth ntaining 1 per cent dextrose was inoculated with cc. of an eighteen hour broth culture and incubated nety-six hours at 37 C. Final p_H was determined olorimetrically on the cell-free supernatant.

Hydrolysis of Sodium Hippurate.—This was determined by the method described by Coffey and Foley.[35] Known positive and negative strains (Lancefield J 17 A4 and O 90R respectively) were included. The results were uniformly negative (table 6). Some of the strains yielded a precipitate on the addition of ferric chloride to the hippurate medium, due to extraneous salts. These precipitates were readily distinguished from ferric benzoate by their solubility in hydrochloric acid.

Toxin Production and Mouse Virulence.—All strains were tested for the ability to produce erythrogenic toxin, according to the methods described by Kirkbride[36] and Coffey.[37] There was no evidence of toxin production (table 6).

Virulence for mice was determined by the intraperitoneal injection of 0.5 cc. of an eighteen hour broth culture into 2 mice, each 15 to 22 Gm. in weight. If mice survived forty-eight hours, the cultures were considered avirulent (for mice). If the mice died, serial dilutions (each dose contained in a volume of 0.5 cc.) were prepared from an eighteen hour broth culture and tested in a similar manner to determine the minimum lethal dose. The results are recorded in table 6. Relatively few (2 per cent) were virulent for mice.

The biochemical activity of group D streptococci does not appear to be correlated with serologic type. The reduction of methylene blue seems to be the only biochemical characteristic common to all group D strains aside from the ability to grow in the presence of 6.5 per cent sodium chloride, as previously reported by Rantz.[38]

COMMENT

Group D is peculiar in that different strains appear to have chemically different type-specific antigens. The antigenic structure of type 2 resembles that of the streptococci of other serologic groups, in which, with the exception of group B, the type-specific antigens seem to be protein-like. The similarity of the chemical nature of the substances determining the group and type specificity of the other three types (table 3) to the chemical nature of the group-specific and type-specific antigens of the pneumococci is of some interest. The occurrence among the streptococci of group D of opposite (with respect to chemical nature) antigenic structures—the one resembling the streptococci and the other the pneumococci—is unique for this serologic group. Additional "pneumococcus-like" charac-

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teristics of group D strains are the tendency to occur as lancet-like diplococci and the ability of some strains to ferment inulin [39]—reminiscent of Migula's classification [40] "Streptococcus pneumoniae"; however, group D organisms do not agglutinate with pneumococcus type antiserums and, with the exception of one or two unverified instances, are insoluble in bile.

As has been pointed out by Frobisher and Denny,[41] all degrees of metabolic gradation may be encountered among the "enterococci," ranging from strains which do not ferment carbohydrates to Streptococcus zymogenes, which utilizes all carbohydrates. That biochemical activity is of limited value in the differentiation of streptococci and in general is not related to antigenic structure is confirmed again by the results of the present study. The reduction of methylene blue appears to be the only biochemical reaction of any value in the differentiation of "enterococci" from other streptococci. As is generally true with the other serologic groups of streptococci (with the exception of group C [24]) there seems to be no valid reason for the differentiation of this group into strains by biochemical characteristics in view of the lack of correlation with serologic group or type.

Physiologic differences between group D organisms and the majority of the strains of other serologic groups is indicated by their resistance to the sulfonamide compounds.[24] Differential growth requirements have not been investigated completely, but there is evidence that group D strains differ from the streptococci of other Lancefield groups [42] and from Streptococcus viridans [43] in minimal nutritional requirements.

It is now generally agreed that not all beta streptococci are hemolytic in the sense that they produce soluble hemolysin. As judged by the tube hemolysis test, it appears that the production of soluble lytic substances is peculiar to strains of Lancefield group A and certain strains of group C.[24] Serologic classification appears to bear out in part McLeod's original contention [26] that strains producing soluble hemolysin were most important in human disease. As suggested by Davis and Rogers,[44] the nomenclature employed to describe blood agar reactions should be adjusted to fit the known facts concerning the biologic differences between strains which produce soluble hemolysin and those strains producing only beta reaction on blood agar. Such a distinction would necessitate the use of the tube hemolysis test in conjunction with standard blood agar, as was recommended by Davis and Rogers,[44] and in the absence of serologic examinations would represent a valuable addition to the diagnostic procedures usually employed in examinations for hemolytic streptococci. The routine procedure of assigning greater diagnostic significance to streptococci producing beta reactions on blood agar (with consequent disregard for alpha and gamma strains), while statistically correct, will lead to frequent errors in individual cases. However, serologic classification eliminates the difficulties associated with inconsistent nomenclatures or unstable biochemical phenomena and should be more widely applied in diagnostic work. The majority of organisms causing human infections are placed in Lancefield group A. However, the increased use of serologic classification has resulted in an ever increasing frequency in the recording of infections due to non-group-A strains.[45] Such a situation increases the difficulties inherent in any attempt at a reliable classification without serologic methods. Although, as already pointed out, selection by beta reaction on blood agar will include nearly all group A strains and many non-group-A strains as well, it will also exclude many strains of other serologic groups which may be of significance. Selection by reaction on blood agar in the present study would have resulted in the classification of only 62.5 per cent of the strains isolated. Serologic examination of all streptococci isolated—alpha, beta and gamma—is essential to establish the presence or absence of any particular strain, especially non-group-A, of streptococci in a given culture.

SUMMARY

The streptococci of group D (Lancefield) may be differentiated into four serologic types by means of precipitation and slide agglutination

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sts with type-specific antiserums produced in bbits. The type-specific substance of three pes appears to be carbohydrate; that of the maining type is protein-like.

The "enterococci" have been shown elsewhere belong to group D. Heat resistance, long held be characteristic of these organisms, appears to unreliable as a criterion for their recognition nce only 10 per cent of the strains studied sur- ved exposure to 62.5 C. for thirty minutes. here was no correlation between heat resistance d serologic type or the inability to ferment annitol. Neither could serologic type be corre- ted by biochemical activity. Sodium hippurate as not hydrolyzed. Final p_H varied from 4.2 4.8. None of the strains produced erythrogenic xin, and relatively few (2 per cent) were viru- nt for mice. All strains studied reduced meth- ene blue. This characteristic may be of limited lue in the differentiation of group D organisms om other streptococci.

Blood agar also is of limited value in the recog- tion of group D strains, since alpha, beta and mma organisms were observed within the oup; blood agar reaction was unstable, and anges from beta to alpha and vice versa were served frequently with laboratory transfer the culture. None of the strains produced luble hemolysin.

It is suggested that the term "beta" as applied the streptococci be qualified to differentiate between those strains producing soluble hemolysin and those giving only beta reactions on blood agar. The term "pseudobeta" might be applied to the later group of strains. Such nomenclature would necessitate the use of the tube hemolysis test in addition to the use of the standard blood agar and in the absence of serologic methods would be a valuable addition to the routine procedures used to identify streptococci in most diagnostic laboratories. There is, however, no adequate substitute for serologic classification. This is especially evident in epidemiologic studies, such as those considered in part II of this study, in which non-group-A streptococci frequently were encountered. The occurrence of different biochemical characteristics among strains of the same serologic group (and type) precludes any attempt at classification by a method which is not based on some characteristic common to all strains. Such inconsistencies among strains of the same group and type, together with variations in blood agar reaction emphasizes the fact that such organisms must possess some fundamental physiologic characteristic which might explain their occurrence in human disease. Serologic classification provides a relatively simple method by which the identity of such strains can be established.

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CELIAC SYNDROME

III. DIETARY THERAPY FOR CONGENITAL PANCREATIC DEFICIENCY

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In the six years which have elapsed since the clinical diagnosis of congenital pancreatic deficiency was first made at the Babies Hospital, 38 patients with this disease, exclusive of the group dying of intestinal obstruction in the neonatal period, have been observed here (table 1). Their cases have provided material for study of understanding and control of the infection of respiratory tract. Correspondingly, the the peutic technics tried out have been of two ty one directed toward discovery of the opti dietary regimen and the other toward con of the infection by chemotherapy. The pres paper is a report of the results of the die

TABLE 1.—*Cases of Congenital Pancreatic Deficiency Seen in the Babies Hospital, 1939-1945*

Case No.	Patient	Sex	First Examined	Age at Onset of Cough	Weight in Gm. at Birth	Weight in Gm. at Nearest 1 Mo.	Weight in Gm. at 3 Mo.	Weight in Gm. at 12 Mo.	Age When Regimen Was Started	Diagnostic Means	Status January 1945, with Age
1	J. R.	M	1/27/39	3 mo.	3,410	.....	.....	10,000	3 6/12 yr.	D. J.	Died, 3 9/12 yr.
2	J. D.	F	4/ 2/39	4 wk.	3,410	(6 wk.) 3,410	4,320	.....	.....	P. M.	Died, 4 mo.
3	J. D.	F	5/18/39	7 wk.	3,920	(6 wk.) 4,600	.....	.....	.....	P. M.	Died, 2½ mo.
4	G. D.	M	6/ 1/39	3 mo.	3,450	(1 mo.) 3,860	3,700	6,050	3 mo.	D. J.	Living, 5 9/12 yr.
5	W. C.	M	12/20/39	4 mo.	2,900	.....	.....	.....	7 mo.	D. J.	Died, 1 7/12 yr.
6	J. R.	F	10/14/39	?	3,860	.....	.....	9,450	1 mo.	D. J.	Living, 6 yr.
7	F. d'E.	M	7/28/40	3½ mo.	4,090	.....	5,120	.....	3 mo.	D. J.	Died, 10 mo.
8	S. K.	M	7/30/40	10 mo.	3,060	.....	.....	4,840	1 2/12 yr.	D. J.; P. M.	Died, 1 8/12 yr.
9	R. E.	M	1/ 1/41	?	2,960	.....	.....	.....	7 6/12 yr. ?	D. J.	Living, 11 9/12 yr.
10	P. B.	F	2/ 1/41	1 wk.	3,300	(2½ mo.) 4,090	.....	.....	.....	P. M.	Died, 4 mo.
11	C. J.	M	2/17/41	? 6 wk.	3,260	(2 mo.) 3,720	.....	6,890	1 4/12 yr.	D. J.	Living, 6 8/12 yr.
12	L. M.	M	3/ 6/41	8 wk.	3,180	.....	3,610	.....	.....	P. M.	Died, 3 mo.
13	M. O.	F	5/ 1/41	6 wk.	3,180	(1 mo.) 3,810	5,450	10,100	6 wk.	D. J.	Living, 3 10/12 yr.
14	C. M.	M	5/ 7/41	3 wk.	2,730	(1 mo.) 3,040	3,160	.....	2 mo.	D. J.	Died, 9 mo.
15	G. d'L.	M	11/13/42	9 wk.	3,950	(2 mo.) 4,290	.....	.....	.....	P. M.	Died, 3½ mo.
16	F. M.	M	2/ 2/42	? 10 mo.	2,220	(2 mo.) 2,490	.....	5,320	12 mo.	D. J.; P. M.	Died, 1 2/12 yr.
17	F. M.	M	2/26/43	1 wk.	2,970	(2 mo.) 3,840	.....	.....	4 mo.	D. J.	Died, 5 mo.
18	J. A.	M	3/ 8/43	2½ mo.	3,890	(7 wk.) 3,640	3,780	.....	3½ mo.	D. J.; P. M.	Died, 10½ mo.
19	M. G.	F	6/ 5/43	3 mo.	.....	.....	.....	.....	8 mo.	D. J.; P. M.	Died, 1 2/12 yr.
20	J. M.	M	6/11/43	3 wk.	2,730	(6 wk.) 3,620	.....	.....	.....	P. M.	Died, 2 mo.
21	I. G.	M	6/22/43	1 6/12 yr.	3,300	.....	5,250	6,650	11 mo.	D. J.	Living, 2 5/12 yr.
22	V. D.	M	8/23/43	?	3,800	.....	.....	.....	5 0/12 yr.	D. J.	Living, 6 11/12 yr.
23	O. P.	M	8/30/43	10 mo.	3,680	.....	6,600	4,750	.....	P. M.	Died, 1 1/12 yr.
24	R. H.	M	11/ 4/43	2 mo.	2,930	(6 wk.) 3,440	4,550	.....	4 mo.	D. J.	Living, 1 10/12 yr.
25	J. M.	F	12/17/43	? 3 mo.	2,390	.....	.....	5,900	2 4/12 yr.	D. J.; P. M.	Died, 2 8/12 yr.
26	P. F.	M	3/16/44	?	3,010	(1 mo.) 3,270	4,740	9,300	5 5/12 yr.	D. J.	Living, 6 8/12 yr.
27	M. G.	F	6/11/44	6 mo.	2,700	(1 mo.) 2,840	4,540	6,530	1 7/12 yr.	D. J.	Living, 3 1/12 yr.
28	J. M.	F	6/15/44	6 mo.	3,010	(1 mo.) 3,350	5,000	9,030	2 9/12 yr.	D. J.	Died, 3 yr.
29	M. N.	F	7/26/44	3 mo.	2,270	.....	.....	6,370	4 2/12 yr.	D. J.	Living, 4 9/12 yr.
30	N. M.	M	8/ 1/44	1 wk.	3,180	(2 mo.) 3,640	.....	.....	8 mo.	D. J.; P. M.	Died 10 mo.
31	E. F.	M	8/ 1/44	6 mo.	3,290	.....	.....	8,140	.....	D. J.	Died, 5 9/12 yr.
32	S. P.	F	9/18/44	3 mo.	3,030	.....	.....	.....	10 mo.	D. J.	Living, 1 7/12 yr.
33	I. R.	M	10/24/44	1 wk.	2,760	(1 mo.) 2,500	.....	.....	.....	P. M.	Died, 1 mo.
34	J. H.	F	11/ 6/44	? 1 6/12 yr.	3,460	.....	.....	8,870	5 11/12 yr.	D. J.	Living, 6 1/12 yr.
35	A. O.	M	12/ 4/44	?	2,520	(1 mo.) 3,300	5,240	10,320	3 8/12 yr.	D. J.	Living, 3 9/12 yr.
36	J. E.	F	12/ 5/44	2 mo.	2,840	(1 mo.) 3,230	3,630	5,480	10 mo.	D. J.	Living, 1 1/12 yr.
37	J. K.	F	12/ 7/44	3 mo.	2,870	(1 mo.) 2,950	3,720	7,730	7 mo. ?	D. J.	Living, 3 7/12 yr.
38	B. D.	F	12/13/44	.....	2,880	(1 mo.) 3,460	4,450	7,200	2 9/12 yr.	C. P.	Living, 2 10/12 yr.

* D. J. indicates assay of duodenal juice for pancreatic enzymes; P. M., postmortem examination, and C. P., clinical pict and analysis of feces.

the pathologic physiology of the disease and of the results of therapy based on an understanding of the underlying lesion. The clinical problems form two groups, those relating to nutritional difficulty and those pertaining to the therapy used in this series of cases and represen experience which will probably not be duplicate since most of the cases were studied before pen cillin became available. The sulfonamide co pounds have proved of limited usefulness in t treatment of this disease, and the partial succe of dietary treatment reported here has been b little affected by chemotherapy, except in the mo recent cases. A preliminary report of exper ence with penicillin will follow.

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n 30 of the 38 cases of the present series the gnosis was made during life on the basis of the ical picture, failure to demonstrate trypsin in duodenal juice [1] and, in most instances, re- ery of a gross excess of fat from the feces.[2] 4 of the remaining cases the disease was recog- ed clinically, but the patients when first ex- ined were too ill to be subjected to duodenal inage; the diagnosis was confirmed at autopsy. 4 cases of the disease, all in young infants, diagnosis was first made on postmortem ex- ination. Of the 30 patients on whom labora- y studies were possible, 13 have died with the ure characteristic of obstruction of the respira- y tract, and the diagnosis was confirmed for 6 on whom postmortem examination was formed. Confidence in the accuracy of the gnosis made during life has thus been amply tained. Seventeen patients survive at the time writing and are being followed. This record survival is not due entirely to the dietary imen, since 3 of the patients first seen during past year survived because of administration penicillin.

The prognosis for the child with pancreatic iciency has been considered hopeless. The gest known survival is fourteen years.[3] A vey of the cases in which a diagnosis of brosis of the pancreas" was made post mortem a series of 5,000 consecutive autopsies at the esbyterian Hospital on subjects over the age 14 years revealed no instance in which the ease might reasonably be interpreted as of ngenital origin; yet in several children's hos- tals a diagnosis of congenital fibrosis of the ncreas is made in approximately 3 per cent all cases in which postmortem examination is rformed.[4] It is fair to say that the infant with ngenital pancreatic deficiency whose condition undiagnosed and untreated will not survive to ult life,[4a] but with appropriate treatment the ognosis should be more hopeful. It has long en possible to maintain pancreatectomized dogs in good health for long periods with adequate dietary therapy.[5] Pancreatectomized adults have sometimes survived for long periods with no treatment other than restriction of dietary fats.[6] The therapeutic problem with infants is made more difficult by the requirements of growth, the lack of previous stores of essential food constituents, such as vitamin A, the limitations of the infant diet and probably also the immaturity of the digestive organs other than the pancreas. These difficulties do not, however, appear insurmountable.

The regimen which is at present followed at the Babies Hospial is based in part on careful laboratory studies which have been or will be reported on,[7] in part on clinical experience of the trial and error variety and in part on hypothesis. It is the result of evolution and may be expected to undergo further change. It is reported on because it has prolonged the life and improved the health of a considerable number of infants and children with congenital pancreatic deficiency.

GENERAL NATURE AND RATIONALE OF THE REGIMEN

1. The caloric intake is high, to allow for the inefficient utilization of food. In order to permit satisfactory growth, the daily requirement varies from about 120 to 180 calories per kilogram of body weight and is usually about 150 calories per kilogram in the second year.

2. The dietary fat is low. Balance studies have shown that from 40 to 60 per cent of the fat given in a normal diet can be recovered from the feces.[7b] Carbohydrate can replace triglycerides, or true fats, as a source of calories but cannot replace all the lipid constituents required for normal nutrition. The patient will absorb a small amount of lipids, and these should be carefully selected so as to provide ample amount of the essential, or probably essential, materials. The diet therefore includes one, or preferably several, eggs per day and a large dose of a concentrated oily preparation containing vitamins A and D. Peanut butter in moderate amounts is allowed to patients who are doing well. The fat in whole cow's milk, whether fresh or evaporated, is some-

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times well tolerated clinically but is not well utilized; breast milk, with its higher fat content, is usually not well tolerated. Milk is given in the form of protein milk to young infants and to those not doing well, and skim milk is given to most infants over the age of 1 year. Fats which are not clinically tolerated are those provided in fried foods, salad oils and gross fat in meat; these fats usually produce an increase in the number of stools and in the number of oily droplets visible in them. Consumption of fat increases the fecal loss not only of fat but of other substances, especially protein.[7b]

3. The protein intake should be approximately double the usual amount for the patient's age. Protein is essential to growth; it is inefficiently utilized by these patients,[8] and, unlike fat, it is well tolerated. Adequate protein retention can be obtainely only by the high protein intake of 6 Gm. per kilogram of body weight per day or more. No peculiarities in the utilization of various food proteins have as yet been demonstrated; the protein given has been in the form of milk, cottage cheese, lean meat, fish and eggs. Young or marasmic infants with this disease tolerate protein milk better than skim milk, and protein milk is sometimes used in spite of its higher fat content.

4. The carbohydrate intake is high, since it must provide the calories usually given as fat, as well as those usually given as carbohydrate. Carbohydrate is given to marasmic infants in the form of dextrose and bananas or banana powder. Most infants who are doing reasonably well tolerate sucrose and utilize it well, since it does not require pancreatic digestion. It is included in generous amounts, and the formula and stewed fruits and other desserts may be used as vehicles for it. Fruits and vegetables of almost all kinds are well tolerated and well utilized. Desserts composed of sugar, eggs, gelatin and sponge cake are useful. Use of hard candies is encouraged. Bananas are not essential but are useful in moderate amounts; if used in excess, they increase the bulk of the stool and the loss of other substances. Two or three a day are usually allowed. Potato or cereal starches in the form of bread, cereal, rice, etc., are given in amounts limited to one serving per meal. These starches are well tolerated by patients over the age of 1 year who are doing well, but they are often poorly tolerated by younger infants or by older children who are doing poorly, and some discrimination is advisable in introducing them. They are utilized fairly well.[7b] One of the chief differences between the optimal diet for children with pancreatic deficiency and that for children with celiac disease is the good tolerance of the patients with pancreatic deficiency for sucrose and for moderate amounts of starch. Dietary glycosuria with normal dextrose tolerance curve is sometimes encountered when the sugar intake is high.

5. Vegetables are given in plentiful amounts. The patient with pancreatic deficiency tolerates roughage and requires a high intake of minerals since the fecal loss of ash is excessive. Several patients who had a hemorrhagic tendency with prolonged prothrombin time had a history of having received a bland diet without many vegetables. Patients who had received a usual amount of green vegetables had a normal prothrombin time. The vitamin content of vegetables also makes them valuable.

6. Supplementary vitamins are given regularly and liberally. Prior to treatment deficiency in vitamins A, D or K has been encountered in a fair number of cases. Preparations of vitamins A and D are given in large amounts. Preparations containing vitamin D in emulsified or other form, without vitamin A, are to be avoided. One instance of vitamin C deficiency has been encountered, but no cases of deficiency of other water-soluble vitamins have been recognized. However, any patient with excessive fecal loss may be expected to lose some of the water-soluble vitamins. It has been our custom to provide vitamin B complex in preparations given by mouth. Liver extract has been administered parenterally to a few young or marasmic infants.

7. Pancreatin has been given, since it has a definite though mild effect on retention of fat, starch and protein.[9] The necessity of providing specific pancreatic substances, such as lipocaic,[10] remains disputed. The patients who are accustomed to pancreatin like it, and only occasional difficulty has been experienced in its administration. It has been given in powdered form, in doses of 1 teaspoon (1.5 Gm.) per meal; it is mixed with cereal, potato, cheese or other convenient solid food. When mixed in the formula, it usually produces curd, and it is administered in this way only to young infants receiving protein milk.

A distinction should be made between this recommended regimen and the one used for the

8. (*a*) Andersen.[7b] (*b*) Shohl, A. T.; May, C. D., and Shwachman, H.: Studies of Nitrogen and Fat Metabolism on Infants and Children with Pancreatic Fibrosis, J. Pediat. **23**:267-279 (Sept.) 1943.

9. Andersen (footnotes 2 and 7*b*). Shohl and others.[8b]

10. Dragstedt, L. R.; Van Prohaska, J., and Harms, H. P.: Observations on a Substance in Pancreas (a Fat Metabolizing Hormone) Which Permits Survival and Prevents Liver Changes in Depancreatized Dogs, Am. J. Physiol. **117**:175-181 (Sept.) 1936.

reated" patients, to be discussed later. The tients seen during the first few years of this udy provided information as to which foods ere contraindicated, as well as to which were ell used, and these patients were not always eated according to present concepts. The reated" patients all received the following mini-al therapy: a low fat, high protein diet; large oses of vitamins A and D, and pancreatin in the nount of at least 3 Gm. a day. Many received tle starch, and some were limited as to sugar d other less essential foods.

Sample diets are given in table 2, to demonstrate the practical application of the principles tlined. The diets have been amply tested. The e for younger infants, with protein milk and nited starch, is also used for older infants who e doing poorly. An attack of diarrhea is an dication for returning temporarily to the low arch, protein milk diet.

TABLE 2.—*Representative Diets for Patients with Pancreatic Deficiency* *

A. Patients Under the Age of 1 Year: 150 Calories per Kilogram of Body Weight

eakfast:
3-4 ounces (90-120 cc.) of fruit juice (orange, grapefruit or tomato) or puréed fruit
1 egg, soft cooked
1 slice of zwieback (may be garnished with jelly)
1 mashed ripe banana if appetite is good
6-8 ounces (180-240 cc.) of formula
1 level teaspoon of pancreatin †

nner:
1-2 tablespoons or more of minced lean meat, broiled, boiled or roasted only
1-2 tablespoons or more of puréed vegetable
1 slice of zwieback (optional)
Dessert: puréed, cooked or canned fruit, gelatin or junket made with skim milk
6-8 ounces of formula
1 level teaspoon of pancreatin

pper:
1-2 tablespoons of pot cheese or meat; the pot cheese may be flavored with honey, jelly or banana powder
1-2 tablespoons or more of puréed vegetable
Dessert, zwieback, formula and pancreatin as at noon

ening: 6-8 ounces of formula

rmula: Calculate to provide two thirds of total calories
Protein milk,† to provide three fourths of formula calories
Banana powder, to provide one fourth of formula calories

tamins: Concentrate of vitamins A and D † sufficient to provide 20,000 U.S.P. units of vitamin A per day, given in two or three doses
Vitamin B complex †
Ascorbic acid, 0.05 Gm., if fruit juice is not well taken

B. Patients Aged 1 to 2 Years

A trial with skim milk is made soon after the twelfth month r patients who are doing well; it is usually well tolerated. sh is tried next. One small serving of starch per meal is ded. The transition to the diet for older infants is made adually

C. Patients Aged 3 to 4 Years and Older

eakfast:
Fruit or fruit juice
½-⅔ cup cooked whole grain cereal with skim milk and sugar
1-2 eggs, prepared in any way except fried
½-1 slice of bread or toast, preferably whole grained, with jelly or honey, without butter
1 or more glasses of skim milk, may be flavored with sugar, cocoa, vanilla, etc.
1 level teaspoon of pancreatin

nner:
Large serving (3-4 teaspoons or more) of lean meat, poultry or fish, broiled, boiled or roasted, all visible fat to be cut off
3 or more tablespoons of cooked vegetables
1 small serving of starch, as potato, rice or macaroni
1 or more glasses of skim milk
Dessert: cooked or canned fruit, gelatin, junket made of skim milk, custard, puddings or sponge cake
1 level teaspoon of pancreatin

Lunch or supper:
Same as dinner, except that pot cheese may be substituted for meat

Between meals:
Any food item included in this list, except starch. Hard candy, sponge cake and arrowroot biscuit may be given

Note.—The child may receive second portions of any item except starch. Any of the allowed foods may be served in the form of soup or frozen desserts, if desired

Vitamins: Same as those given the first year

D. General Instructions

Rules for parents:

1. Include only the foods on the list.
2. Do not serve raw vegetables and fruits other than orange, grapefruit, apple, banana, pear, peach and lemon juice.
3. Do not use any packaged food of which you do not know the ingredients or which contains substances not on the allowed list.
4. Do not use flour, corn starch, etc., in the preparation of food without reducing the feeding of starch.
5. Remove all visible fat on meats; broil, boil or roast only.
6. Do not use fats or oils of any kind in the preparation of food.
7. Use only milk which is commercially skimmed. It is not enough to pour the cream from the top of a bottle of whole milk. Use 1 quart (1 liter) daily.

Foods Allowed

Meats	Vegetables	Fruits
Beef	Tomato juice	Strained orange juice
Lamb	String beans	Pineapple juice
Veal	Squash	Grapefruit juice
Liver	Carrots	Grape juice
Kidney	Peas	Lemon juice
Chicken	Asparagus	Lime juice
Turkey	Cauliflower	Juice of berries
Fish	Beets	Bananas
Shellfish (oyster, clam, shrimp, crab, lobster)	Spinach	Scraped or peeled apples, pears and peaches
	Mushrooms	Cooked or canned apples, apricots, pears, peaches, pineapple
	Onions	
	Beet greens	
	Eggplant	
	Broccoli	Strained cranberry juice

Starches: 1 Serving per Meal Only	Miscellaneous
Bread, preferably whole-grained	Egg
Potato, rice, noodles, macaroni, spaghetti	Pot cheese
Lima beans, if potato, etc., are omitted	Soup without fat
Split peas, if other starch is omitted	Jelly or jam without seeds
	Marshmallows
	Sugars—white sugar, brown sugar, corn syrup, honey, maple sugar, molasses
	Lollipops or hard candy
	Fruit ices
	Cake without fat—sponge, angel food
	Gelatin
	Cocoa
	Junket
	Custard, including frozen foods

Foods Not Allowed

Meats and Fats	Miscellaneous
Butter, oleomargarine	Raw vegetables or fruits not on list
Fat meats, bacon, pork	Luncheon meats, salami, etc.
Lard, Crisco, Spry	Cream candies, chocolates
Fried foods	Crackers
Cream, whole milk	Cookies, doughnuts, pie
Peanut butter	Gravy with fat or flour
Cheese other than pot cheese	Corn
Chocolate	Beans—navy or kidney
Salad oils, olive oil, mayonnaise	Cake containing fat
Duck or goose	

For older children, add the following, if trial shows toleration: salads, melons, berries, small amounts (1 teaspoon) of peanut butter, a few nuts, preferably as flavoring

* Miss Emma Mike and Miss Eleanor Dasch, dietitians at the Babies Hospital, aided in planning the menus and in testing the individual foods.

† A variety of suitable preparations are available. The following preparations were chiefly used in the present series of cases:

Pancreatin: A preparation obtained from Eimer and Amend, New York, and preferred because of its high lipase content.

Vitamins A and D: Percomorph liver oil (Mead Johnson and Company, Evansville, Ind.); haliver oil (Abbott Laboratories, North Chicago, Ill.).

Vitamin B complex: Oral B complex (Lederle Laboratories, Inc., Pearl River, N. Y.) 2 teaspoons once a day.

Protein milk: Two preparations were used. Protein Milk (Mead Johnson and Company) seems to be better tolerated by the marasmic patient; Hi-Pro (Special Milk Products, Inc., Los Angeles) is more acceptable to older infants, because it is sweet and is well tolerated by infants in fair or good condition. The fat content of the latter is lower.

EVALUATION OF THE RESULTS OF DIETARY THERAPY IN TERMS OF SURVIVAL

An estimate of the success of dietary therapy is difficult, for several reasons: (1) the variable course of the disease and length of survival of both untreated and treated patients; (2) the differences in the age of the patient and the stage of the disease at which therapy is begun; (3) the variation in the degree of intelligence, care and confidence with which the regimen is carried out, and (4) the fact that many patients are still living when the present paper is being written and that therefore the ultimate course of their disease has still to be observed.

The two criteria which most nearly fulfil the requirements are the age at which a cough was first noticed and the weight curve during the first year of life. An attempt has been made to analyze the cases of the present and of the previous series with respect to the age at which the patient was first known to have a persistent cough, which will be hereafter referred to as the age of first cough. This information has been correlated with the early weight curve, the period of survival and the apparent efficacy of therapy.

1. *The Age of First Cough in Relation to Period of Survival.*—Those cases in the series based on postmortem data, reported in 1938,[4a] in

TABLE 3.—*Relationship of Age of First Cough to Period of Survival of Untreated and Treated Patients with Congenital Pancreatic Deficiency*

A. Untreated Patients from Series Reported in 1938

Age at First Cough, Mo.	Number of Patients	Number Dying at Age				
		Under 3 Mo.	3-6 Mo.	6-12 Mo.	1-5 Yr.	Over 5 Yr.
0-1	5	3	1	1	0	0
1-2	6	3	2	0	1	0
2-3	1	0	1	0	0	0
3-6	8	0	3	4	1	0
Over 6	16	0	0	6	8	2
Total	36	6	7	11	10	2

B. Present Series, January 1939-January 1945

Age at First Cough, Mo.	Number of Patients	Number Dying at Age					Number Living	
		Under 3 Mo.	3-6 Mo.	6-12 Mo.	1-5 Yr.	Over 5 Yr.	1-5 Yr.	Over 5 Yr.
0-1	7	3	2	2	0	0	0	0
1-2	6	1	2	0	0	0	3	0
2-3	8	0	0	1	3	0	2	2
3-6	5	0	0	1	2	1	1	0
Over 6	12	0	0	0	3	0	3	6
Total	38	4	4	4	8	1	9	8

C. Direct Comparison of Survival of Early and Late Cases in the Two Series

Onset of First Cough	Series	Number of Patients	Patients Who							
			Died Under 1 Yr.		Survived 1 Yr.		Survived 5 Yr.		Are Living at Over 1 Yr.	
			Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
Early	1938	20	18	90	2	10	0	0	0	0
	1945	26	12	46	14	54	3	11.5	8	31
Late	1938	16	6	37.5	10	62.5	2	12.5	0	0
	1945	12	0	0	12	100	6	50	9	75

The wide differences in the time of survival of the untreated patients have been pointed out.[4a] In the majority of patients death occurred before the age of 1 year, but a fair number survived for various periods, up to 14 years, and showed various degrees of retardation, digestive symptoms and infection of the respiratory tract. The criterion which I previously suggested for separation of the cases of early development of the disease (group II) and the cases of late development (group III) was the age of the patient at death, whether over or under 6 months. This is an objective criterion, which is satisfactory for a study of postmortem data. For the clinical purposes of prognosis and evaluation of therapy some other standards are required which are based on data obtainable in vivo, and preferably during the early course of the disease.

which the age of first cough was recorded have been compared with the cases of the present series with respect to the age of first cough and the age at death. In the present series no distinction is made between the treated and the untreated patients, in order to obtain an impression of the over-all effect of present knowledge of prognosis. A correlation between the age of first cough and the age at death is apparent in both series (table 3). None of the infants who showed respiratory symptoms during the first month of life have survived (fig. 1 *A* and *B*). However, the prognosis for infants whose respiratory symptoms first appeared in the second month or later seems to have improved in the second series (table 3). Of the 3 survivors from the group with first cough before 2 months, 2 have at the time of writing severe infections of

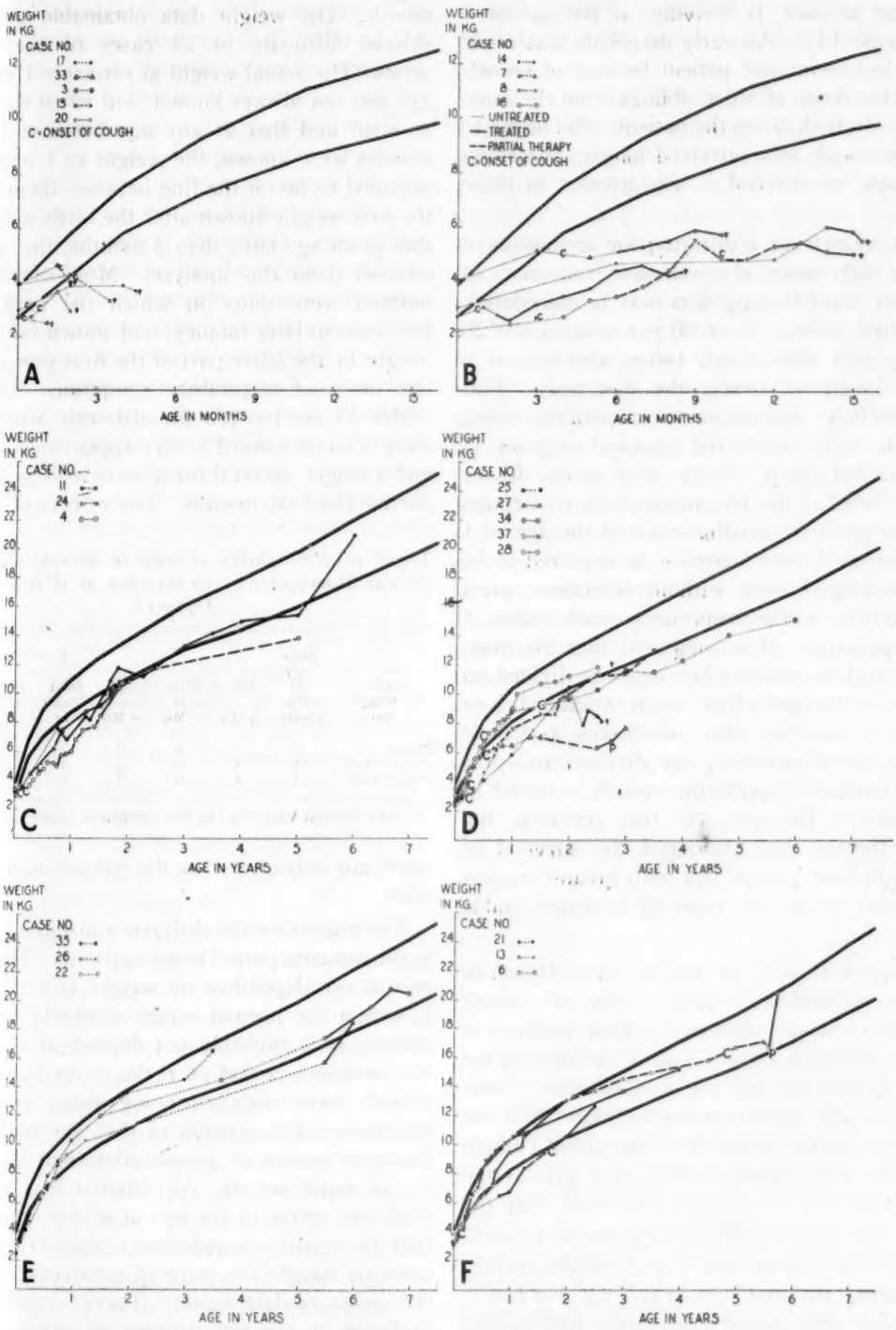

Fig. 1.—*A*, growth curves of untreated patients with early appearance of cough. The heavy lines mark the tenth and the ninetieth percentile of the weight of normal male infants.[14] *B*, growth curves of treated patients with early appearance of cough. The heavy lines mark the tenth and the ninetieth percentile of the weight of normal male infants.[14] *C*, growth curves of boys first treated after onset of cough but before the age of 2 years. The heavy lines outline the range for two thirds of normal boys.[14] In this graph, and in *D* and *F*, *P* indicates penicillin therapy. *D*, growth curves of girls surviving the first two years without treatment. The heavy lines outline the range of weight of two thirds of normal girls.[14] *E*, growth curves of boys surviving the first two years without treatment. The heavy lines outline the range of weight of two thirds of normal boys.[14] *F*, growth curves of 2 girls (cases 6 and 13) and 1 boy (case 21) who received dietary therapy before the onset of chronic cough. The heavy lines outline the range of weight of two thirds of normal girls.[14]

the respiratory tract and an uncertain prognosis (cases 24 and 36), while the third, who received treatment at once, is thriving, at the age of 4 years (case 13). An early diagnosis was made for the last-mentioned patient because of knowledge of the death of older siblings from the same disease. In both series the patients who began to have the cough later survived longer; the effect of therapy on survival is also greater in these patients.

In the search for a criterion for separation of cases of early onset of the disease from cases of late onset, the following data may be considered. In the first series, 18, or 90 per cent, of the 20 patients with first cough before the age of 6 months failed to survive the first year. This group includes the majority of patients dying before the sixth month and classified as group II in my earlier paper. In the first series, 10, or 62.5 per cent, of the 16 patients with first cough after the age of 6 months survived the age of 1 year. Survival may therefore be expected to be more prolonged even without treatment when the infection of the respiratory tract makes a later appearance. It is suggested that the cases of early and the cases of late onset be divided on the basis of the age of first cough, whether before or after 6 months; this substitutes a clinical criterion for an arbitrary age division and provides a basis of classification which is useful in evaluation of therapy. By this criterion, the dietary therapy has prolonged the survival of patients in both groups, but with greater success in the later group, as might be expected (table 3 *C*).

2. *Gain in Weight During the First Month in Relation to Survival.*—When charts of growth curves were being prepared for these patients, it became obvious that there is wide variation in the rate of growth during the first months of life, even before the appearance of a cough. It is not surprising that the infants who contracted a cough during the first month showed poor gain at the age of 1 month. It appears, however, that the infants who gained poorly during the first month as a rule acquired an infection of the respiratory tract during the first half year (fig. 1 *A* to *C*), while those who gained moderately well during the first months began to cough later (fig. 1 *D* to F). In order to test the accuracy of this impression, an attempt was made to correlate the gain during the first month with the age at onset of first cough and with the length of survival. Assuming that 700 Gm. approximates the normal average gain during the first month, the cases were classified as to whether there was no gain, a gain of less than 350 Gm. (one-half normal) a gain of more than 350 Gm. during the fi month. The weight data obtainable were co sidered adequate in 24 cases of the prese series. The actual weight at precisely 1 month age was not always known; but when the weig at birth and that at any age between 1 and months were known, the weight at 1 month wa assumed to lie on the line between them. Whe the first weight known after the birth weight wa that at an age later than 3 months, the case wa omitted from this analysis. Most of the cas omitted were those in which the patient wa first seen in later infancy, had shown fair gain weight by the latter part of the first year and ha late onset of respiratory symptoms. The da (table 4) are too few for elaborate analysis b show a trend toward a later appearance of coug and a longer survival for infants who gained we during the first months. The effects of therap

TABLE 4.—*Relationship of Gain in Weight During t First Month of Life to the Age at Which Cough Appears* *

Gain in First Mo.	Number of Patients	Age at First Cough			Fate of Patient		
		<3 Mo.	3-6 Mo.	>6 Mo.	Died Under 1 Yr.	Died After 1 Yr.	Livi
None.....	5	5	0	0	5	0	0
<½ normal..	13	8	3	2	7	3	3
>½ normal..	7	4	0	3	1	0	6

* The normal gain for the first month is taken at 700 Gm.

were not considered in the preparation of th table.

The reason for the difference in rate of growt in the neonatal period is not apparent. The differ ence is not dependent on weight at birth, whic is within the normal range in nearly every in stance. It is probably not dependent on diet i the neonatal period, for the formulas, thoug varied, were usually among those considere satisfactory for patients of that age and no in stance is known of grossly abnormal feeding i the neonatal period. An attempt was made t study the effect of the age at which administra tion of vitamin supplements was begun; th came to naught for want of satisfactory data i the cases of late onset. There is as yet n evidence of varying degrees of pancreatic de ficiency in patients presenting the clinical symp toms of congenital pancreatic deficiency, a judged by the amount of trypsin demonstrab in the duodenal juice.[1] Most of the growt curves suggest those of animals fed on deficien diets, a fact which is not surprising. The od finding is the wide variation in these curves. Tw explanations suggest themselves. The first is th

sibility that there may be differences in iciency of function of other digestive organs, h as the stomach or the small intestine. The ants having good function of all parts of the estive tract other than the pancreas might be pected to gain better than those who had in- ient function at several steps in digestion. The ervation that some infants with congenital ncreatic deficiency show concretions in the estinal glands, as well as in the pancreas, is ggestive.[11] A second hypothesis compatible h the facts known is that the infants are born h variable stored amounts of some essential d factor or factors which they are unable to ain in adequate amounts from their food in absence of pancreatic function. Confirmation this hypothesis is difficult, since it requires, ong other things, an accurate dietary history of mother during pregnancy and observations the effect of dietary therapy in the neonatal iod, both extremely difficult to obtain. There no evidence as to what food factor might be olved; vitamin A fulfils the conditions, and the sibility that it is the lacking factor should be estigated. The fact that most of the infants n at a slower rate than is normal from birth, n prior to the appearance of symptoms of olvement of the respiratory tract, is evidence favor of the view that the pancreatic lesion present at birth and the infection of the respira- y tract is a sequela. It seems improbable t the lesions of the pancreas and those of the piratory tract arise simultaneously from an ection acquired postnatally.

In most patients who survived the first year gain in weight during the first year was slow, the majority were farthest below normal at ut the end of the first year (fig. 1 *C* and *D*). ring the second year growth often continued a steady rate, so that by the age of 2 years weight lay near or within the normal range. rvivors over the age of 2 years, whether treated untreated, have weights, and also heights, ich are in the lower part of the normal range, h a few exceptions (fig. 1 *C* to *F*). Knowl- e of this straight, but ascending, weight curve several practical implications: 1. It suggests etter prognosis as to growth for those patients o are first seen at 10 or 12 months of age than ir retardation at that time would seem to tify. 2. Lack of gross retardation after the e of 2 years is consistent with the diagnosis of ncreatic deficiency. 3. The pride of the physician in the good growth of treated patients is somewhat deflated. The valid criterion of successful therapy is control of infections of the respiratory tract and continued health of the patient.

3. *Type of Infection at Time Dietary Therapy Is Begun.*—In the foregoing discussion reference has been made to "first cough," as though this symptom were always of the same type and severity. It is a common observation, however, that a chronic cough, without or with bronchiectasis, may be present for weeks, months, or even years, before an overwhelming suppurative bronchitis supervenes. When this occurs, the course becomes fulminating, and death results from asphyxia because of the thick mucopurulent material which fills the bronchial tree and the trachea (fig. 1 *D*, cases 25 and 28). This purulent bronchitis is marked by hyperpnea, emphysema and attacks of cyanosis, often relieved by coughing. No lasting improvement has resulted from dietary therapy alone begun after the appearance of suppurative bronchitis. In the present series, 15 patients were first seen after the onset of suppurative bronchitis; the 9 who received dietary treatment alone or in combination with sulfadiazine died within a few days or weeks. Recently it has been possible to obtain penicillin for these patients, and experience with it will be reported later.

Dietary therapy begun several weeks or months after first cough but before the appearance of the symptoms of suppurative bronchitis has had varying results, the most common one a gradual gain in weight and height with gradual improvement and ultimate disappearance of the cough (fig. 1 *C*, *D* and *E*). If a patient is undernourished when first examined, his gain in weight in the first few months may be rapid. The latter course of these patients remains to be observed, and may be presumed to depend largely on the presence and degree of bronchiectasis. Several patients who had a deep and hyperresonant thorax when first seen had no demonstrable abnormalities after a long period, of one or several years, without chronic cough. The following case illustrates an unexpectedly good result after severe early infection, and in spite of intermittent therapy.

Case 11.—C. J., a boy, is at the time of writing 6 years and 2 months of age. He is the fourth of 6 brothers. None of the siblings give evidence of pancreatic deficiency, and the younger siblings have been shown not to have steatorrhea.[12]

11. Farber, S.: Pancreatic Function and Disease Early Life: V. Pathologic Changes Associated with ncreatic Insufficiency in Early Life, Arch. Path. **37:** 50 (April) 1944.

12. Dr. John Monfort, of the Norwegian Hospital of Brooklyn, provided the earlier part of the following record.

The patient was born normally at term, with a weight at birth of 7 pounds 3 ounces (3,260 Gm.). He was breast fed and was given a supplementary formula for five weeks, after which he received a formula of whole milk and dextrimaltose. Administration of supplements of orange juice and cod liver oil was begun at 7 weeks. He was admitted to the Norwegian Hospital at the age of 8 weeks because of mild diarrhea, consisting of five to six green stools daily, and failure to gain weight on an adequate formula. His weight was 8 pounds 3 ounces (3,713 Gm.). The positive physical signs of the disease were undernutrition and mild pharyngitis. Roentgenograms of the chest showed exaggerated hilar markings. After two weeks the pharyngitis improved, and the stools decreased in number to three or four daily; they became large and foul. Pancreatic deficiency was not suspected, but steatorrhea was discovered; and, after several changes of formula, the patient began to gain weight on a diet of skim milk, bananas, melitose, calcium caseinate and lactic acid. He was given 15 drops of percomorph liver oil. By the fourth month he was receiving vegetables, potatoes and pot cheese. By the age of 8 months egg and meat had been added. During his five months' stay in the hospital he had frequent colds, bronchitis and otitis media. He was discharged from the hospital in improved condition. Four months later he was readmitted, because of loss of weight, bronchitis and diarrhea. On this admission a distended abdomen and a protruding umbilicus were noted. He improved on a high protein, low fat diet. The following month he was sent to a city hospital for contagious diseases because he was thought to have pertussis. From there he was transferred to a convalescent home. He returned home at the age of 16 months, but after a few days he was readmitted to the Norwegian Hospital. During all these migrations he remained on a regimen planned for patients with celiac disease. On the last admission his case was reviewed. A diagnosis of celiac disease was first made, and the possibility of pancreatic deficiency was also considered. The latter diagnosis was confirmed, with the cooperation of our laboratory. His diet was altered only by the addition of pancreatin and an increase in the vitamin supplements.

The patient was admitted to the Babies Hospital for further study, at the age of 27 months. At this time he was well nourished but small for his age, with a weight of 11.2 Kg. and a height of 87 cm. His abdomen was moderately prominent (fig. 2 *A*), and he had a chronic, dry cough. Coarse rales were audible on auscultation. A roentgenogram of his chest showed increased bronchovascular markings in the perihilar regions, extending down to the diaphragm bilaterally. The balance study [7b] was terminated by the appearance of measles in the ward, which the patient acquired. He was transferred once more to a hospital for contagious diseases.

During the next year he was seen at irregular intervals at the Vanderbilt Clinic; he showed a gradual gain in weight and little other change. At the age of 3½ years he was again in a hospital for contagious diseases, with the diagnosis of pertussis. At the age of 4 years he underwent a herniotomy at the Norwegian Hospital.

His second admission to Babies Hospital was in April 1943, at the age of 4½ years, because of unusually poor gain in weight during the preceding winter. On this admission he gave a history of repeated prolapse of the rectum. He was also said to have a "bad day" about once a month, characterized by mild diarrhea, with five or six stools a day. He had had an occasional cough, but no colds, during the winter. Physical examination showed that the boy was undersized, with poorly developed muscles and a large abdomen. His physical condition had deteriorated, as shown in his photograph (fig. 2 *B*). He had presumably been on his prescribed diet, but there were probably omissions, chiefly for economic reasons. The roentgenographic findings were similar to those on his previous admission. During his stay in the hospital further studies were made. He was discharged to a convalescent home.

During the following year his condition improved gradually. Last summer, when he was 5½ years old, he was in a camp where his diet was supervised, and his improvement was rapid (fig. 2 *C*). At the time of writing, he has no cough, and his lungs are normal on physical examination. He is retarded in growth but by no means in activity, and his morale is unimpaired, in spite of his having spent a large proportion of his life in hospitals. He has a somewhat enlarged abdomen; the physical findings are otherwise normal. His growth curve is given in figure 1 *C*. It shows an irregular course, especially during the several early attacks of "pertussis."

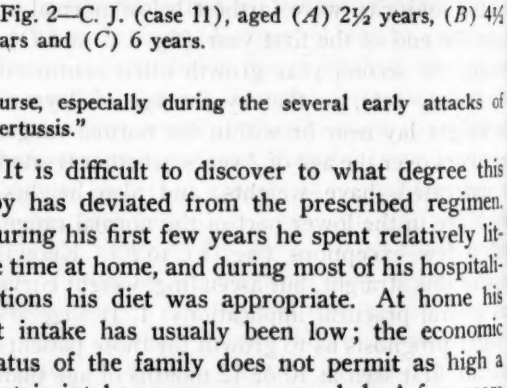

Fig. 2—C. J. (case 11), aged (*A*) 2½ years, (*B*) 4½ years and (*C*) 6 years.

It is difficult to discover to what degree this boy has deviated from the prescribed regimen. During his first few years he spent relatively little time at home, and during most of his hospitalizations his diet was appropriate. At home his fat intake has usually been low; the economic status of the family does not permit as high a protein intake as was recommended. A few years ago he was known to be an "ice box stealer," and it is unlikely that he has reformed. A preparation of vitamin A supplement has been given, though irregularly, and much of it has been donated. However, the mother of the family believes that all of the boys should share this supplement when any is available, and so the

patient's portion is limited. The mother has done her best to purchase the vitamin A supplement at least at intervals. Pancreatin has been provided regularly through the social service department of the Babies Hospital and has undoubtedly been taken most of the time, as the boy considers a meal tasteless without it. It is interesting that the patient has continued to improve on this somewhat intermittent therapy, with frequent, but never prolonged, lapses.

The 3 infants for whom the diagnosis was correctly made before or immediately after the first cough all did well under dietary therapy as long as they were kept on the regimen. In the cases of 2 of these patients relaxation of therapy was followed after a time by pneumonia; their cases (6 and 21) are summarized in the discussion of partial therapy. The child (M. O., case 13) who has been maintained on the regimen since within a week of her first cough, at 6 weeks of age, lost her cough promptly and has since remained free from cough to her present age, of nearly 4 years. Her case was briefly abstracted in connection with a previous report on balance studies.[7b] It may be of interest to record the means of diagnosis and the early treatment of this child.

Case 13.—M. O., a girl, was the product of a sixth pregnancy. The first infant, a boy, died of congenital atresia of the small intestine and was found at postmortem examination to have fibrosis of the pancreas. His case was reported in the study of the first series (case 3) [I]).[4a] The second child, a girl, began to have a cough at the age of 12 days and died at the age of 33 days, of bronchopneumonia. The third pregnancy resulted in a miscarriage; the fourth, in a normal girl, and the fifth, in a boy, who had frequent stools from birth, began to cough at 6 weeks of age and died of bronchopneumonia at 10 weeks of age. Postmortem examination (done elsewhere) revealed bronchitis due to staphylococcic infection, but the pancreas was not examined.

The patient was born normally at term, with a weight of 7 pounds ¼ ounce (3,182 Gm.) at birth. During the neonatal period she had seven or eight stools a day, which appeared normal. She gained slowly, and at 6 weeks of age a cough developed, which after a few days was sufficiently severe to produce attacks of cyanosis. At this point the mother took the infant to a pediatrician, saying, "This child has whatever the others had; can you do something about it?" The physician made the diagnosis of pancreatic deficiency on the basis of the family record and the physical findings, though he was unaware of the discovery of pancreatic fibrosis in the first boy. He gave the infant a formula containing protein milk; he also gave sulfathiazole, in a dose of 0.6 Gm. per day, and recommended strict isolation. During telephone consultation I suggested the addition of large doses of a preparation of vitamin A given orally and of a preparation of vitamin B complex and liver extract given parenterally, the parenteral therapy to be discontinued after a few weeks. It was agreed that hospitalization would increase the danger of further infection and would not contribute to the therapy. The infant promptly began to gain in weight, and the cough disappeared in a few weeks. At the age of 7 weeks she had slight vaginal bleeding, which ceased after the administration of a preparation of vitamin K. Use of solid foods was begun early, of vegetables at 2 months and of puréed fruits, bananas and scraped liver in the third month. When the patient had reached 6 months of age, her diet included all solid infant foods other than cereals. The latter were added in moderate amounts at about the age of 1 year.

At the age of 6 months the infant was seen at the hospital for a few hours; during this time a duodenal drainage was performed; analysis demonstrated the absence of pancreatic enzymes. The patient remained in isolation at home, with the exception of this incident, until about the age of 1 year. Her development was normal and her health excellent. At this time it seemed essential for her normal development that she begin to have social contacts, and the parents had the courage to risk the exposure to infection that was involved.

Fig. 3.—M. O. (case 13), aged 3 years.

Since then she has had the usual contacts of family and playground. Although she has had occasional colds, they have never been prolonged, and she has not had bronchitis. Her diet is now limited only as to fat intake. She receives with each meal pancreatin and capsules containing preparations of vitamins. Clinical intolerance to fatty foods (including ice cream) has been shown by a few loose stools and somewhat diminished activity for a day, but in the last year this symptom has decreased. Physical examination shows no abnormalities at the time of writing other than a somewhat prominent abdomen (fig. 3). Her height and weight have continued to be normal for her age (fig. 1 *F*; table 5).

The following summary may be made of the observations on the effect of the degree of infection on the success of dietary therapy. When therapy was begun before or immediately after the first cough, the cough failed to appear or soon disappeared, and no further bronchitis de-

veloped as long as the patient remained on the regimen. When a chronic cough was present but suppurative bronchitis was not, growth was somewhat delayed; but there was gradual improvement, and often final disappearance of the cough. When dietary therapy was begun after the chronic cough was complicated by purulent staphylococcic bronchitis, there was sometimes a temporary gain in weight, and possibly some prolongation of life, but the fatal outcome was not averted.

EVIDENCE AS TO THE RESPECTIVE VALUES OF A LOW FAT DIET, VITAMIN A THERAPY AND PANCREATIN

For various reasons, the recommended regimen has sometimes been followed only in part, a fact which permits some observation on the effect of omission of one or more of the factors. The cases in which such omission occurred will be briefly abstracted.

Table 5.—*Present Status of Living Patients, January 1945*

Case No.	Patient	Sex	Age, Yr.	Age When First Examined	Most Recent Records: Age, Yr.	Weight, Kg.	Height, Cm.	Status January 1945: Normal Activity	Cough	Bronchiectasis	Sinusitis
4	G. D.	M	5 9/12	3 mo.	5	13.9	98	No	+	+	+
6	J. R.	F	6	8 mo.	5 10/12	16.7	111	Almost	—	—	—
9	R. E.	M	11 9/12	7 8/12 yr.	11 9/12	29.6	140	No	+	+	+
11	O. J.	M	6 2/12	1 4/12 yr.	6	21.1	111	Yes	—	—	—
13	M. O.	F	3 10/12	6 wk.	3 9/12	19.2	100	Yes	—	—	—
21	I. G.	M	2 5/12	9 mo.	2 5/12	12.6	85	Yes	—	—	—
22	V. D.	M	6 11/12	4 6/12 yr.	6 11/12	20.5	116	Yes	—	? mild	+
24	R. H.	M	1 10/12	8 mo.	1 10/12	10.1	79	Yes	+	?	?
26	P. F.	M	6 8/12	5 5/12 yr.	6	18.6	109	Yes	Mild	? mild	+
27	M. G.	F	3 1/12	2 6/12 yr.	3 1/12	7.7	82	No	+	+	?
29	M. N.	F	4 9/12	4 6/12 yr.	4 9/12	16.5	90	Yes	+	?+	?
32	S. P.	F	1 7/12	1 5/12 yr.	1 5/12	8.2	..	Yes	+	?+	?
34	J. H.	F	6 2/12	5 11/12 yr.	6 2/12	15.9	104	Yes	+	—	?
35	A. O.	M	3 9/12	3 6/12 yr.	3 9/12	16.0	98	Yes	Mild	—	+
36	J. E.	F	1 1/12	11 mo.	1 1/12	5.5	86	No	+	?	?
37	J. K.	F	3 7/12	3 6/12 yr.	3 6/12	13.1	90	No	Mild	—	?
38	B. D.	F	2 10/12	2 9/12 yr.	2 10/12	8.8	88	No	+	?+	?

1. *Normal diet with whole milk, pancreatin and vitamin A; change to diet for patients with celiac disease; later omission of vitamin A.*

Case 4 (G. D. [figs. 4, 1 *C*]).—The early course of the disease of this boy has previously been recorded.[13] This case was the first of the present series in which the disease was recognized in early infancy, and within a few days of the first cough. The patient was first seen at the age of 3 months, because of failure to gain weight. The conspicuous finding on physical examination was the extreme degree of emaciation. There was an occasional mild cough, but no abnormalities were discovered on examination of the chest. The patient was first seen before experience with dietary therapy had been accumulated and was treated in a manner which would not now be considered optimal. At the age of 3 months his response to administration of pancreatin and vitamin A while he was on a whole milk formula was at first dramatic,[13] and he gained well for about two months. At the age of 6 months, however, bronchopneumonia developed, from which he recovered slowly. His gain was then slow but became more rapid at the age of 9 months, after he was given protein milk in place of whole milk, together with a diet high in protein and low in fat and sugar. During the next year he did fairly well and was seen only at rather long intervals, because his home was at some distance from this city. He was readmitted to the hospital at the age of 26 months, because of increase in his cough during the preceding winter. His weight was 10.2 Kg. and his length 80 cm. Physical examination of his chest revealed nothing of significance, but a roentgenogram showed a patchy increase in density in the hilar regions. He was given sulfathiazole and improved gradually. His leukocyte count remained high, however, ranging from 13,400 to 20,400 per cubic millimeter, with 61 to 71 per cent polymorphonuclear leukocytes. When he was discharged from the hospital after a two weeks' stay, the leukocyte count was 18,100, in spite of his clinical improvement. He was seen occasionally during the next year, during which he did well (fig. 4 *A*). The family then moved still farther away, and the patient was next seen at the age of 5 years. During this interval pancreatin was omitted from his diet. Trials with whole milk and fats resulted in loose stools, and consequently his dietary fat was kept low, although his diet was otherwise liberal. He was kept on a protein milk formula until the age of 4½ years, when skim milk was substituted. At the age of 3 years the use of fish liver oil concentrate was discontinued, and an emulsified preparation of vitamin D containing no vitamin A was substituted. During this period he had three more bouts of pneumonia, at the ages of about 3, 4 and 4½ years. He was next seen at the age of 5 years (fig. 4 *B*), when he presented the characteristic signs of bronchiectasis.

This patient differed somewhat from the others in the series in that in spite of early diagnosis his early treatment was far from ideal; moreover, he not only experienced but survived five periods of pneumonia. When his record is compared with the others, it seems improbable that he would have survived infancy untreated; on the other hand, he might well have avoided his infections if therapy had been more appropriate and consistent. During the early course of the disease he should have received a low fat diet in addition to a preparation of vitamin A and pancreatin;

13. Andersen, D. H.: Cystic Fibrosis of the Pancreas, Vitamin A Deficiency and Bronchiectasis, J. Pediat. **15**:763-771 (Dec.) 1939.

during the second and third years, when therapy included the prescribed diet and supplements, he did well. The lesson to be derived from his later course appears to be that a low fat diet should be accompanied with administration of vitamin A and probably of pancreatin.

2. Low fat, high protein diet with pancreatin but without vitamin A supplement.

CASE 21 (I. G. [fig. 1 *F*]).—This boy was first seen at the age of 10 months, because of attacks of dyspnea and large foul stools. The differential diagnosis lay between asthma and pancreatic deficiency, and it was finally agreed that he was suffering from both maladies. Because of the asthma, he had been kept in strict isolation at home and had not had coryza or cough. Asthmatic attacks were consistently produced by ingestion of certain foods, including orange juice and fish

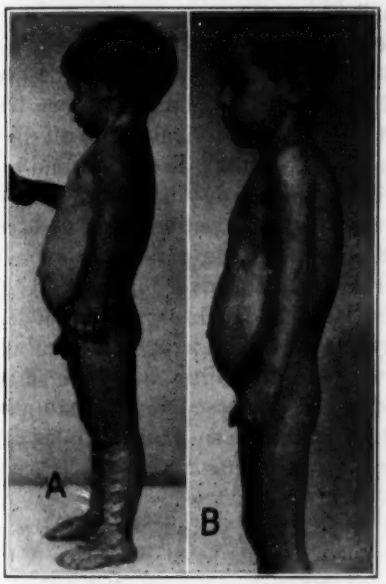

Fig. 4.—G. D. (case 4), aged (*A*) 3 years and (*B*) 5 years.

oils, and some difficulty was experienced in working out a regimen which fulfilled the requirement for therapy of both diseases. It was suggested that a preparation of vitamin A in corn oil (Squibb) be used as a source of vitamin A. This advice was not followed, however, and from the age of 12 months on he received no vitamin A supplement until he had pneumonia, at about the sixteenth month. He was then given approximately 40,000 U. S. P. units of vitamin A in corn oil daily. He recovered from the pneumonia without sequelae and has subsequently done well. The asthma has decreased, and he is free from infection of the respiratory tract. His present weight, at the age of 2½ years, is 12,600 Gm.

3. Successful therapy for several years, with later abandonment of low fat diet and of pancreatin but with continuation of vitamin A therapy.

CASE 6 (J. R. [fig. 1 *F*]).—During the first few years of her life the patient was under the care of one of my colleagues, who made the diagnosis of pancreatic deficiency on the basis of the clinical findings, including marked steatorrhea, and the fact that an older sibling was found to have the disease on postmortem examination. The patient was placed on a low fat diet with vitamin A and pancreatin at the age of about 2 months. Whole milk and a normal diet for infants were gradually substituted at about the sixteenth month. Butter and meat fats were found to produce loose stools, and these were withheld. Administration of pancreatin was discontinued at about 3 years of age. Use of a preparation of fish liver oil was continued, the daily dose containing 10,000 to 15,000 U. S. P. units of vitamin A. The child did well and was free from infection of the respiratory tract until her fifth winter, when she had a chronic cough, followed by bronchopneumonia in the spring. She was admitted to the Babies Hospital the following October, at the age of 5½ years, with chronic bronchopneumonia but without evidence of bronchiectasis. On this admission the diagnosis of pancreatic deficiency was confirmed by laboratory studies. She responded to penicillin therapy, and her lungs have become clear, as shown on physical and roentgenographic examination. At the time of writing she is again on the regimen, has good health and is in school.

4. Low fat diet without other restrictions or vitamin supplements.

Five of the children whose pancreatic deficiency was first correctly diagnosed when they were 3 years of age or older had been placed on a low fat diet during later infancy on empiric grounds and were maintained on it because addition of fat to the diet resulted in loose stools (cases 1, 9, 22, 35 and 38; fig. 1 *E*). Only 1 of them had been given a vitamin A supplement consistently after the first year. All belonged to the group with late cough, but all had a chronic cough when first seen. It is probable that the reduction of dietary fat relieved the symptoms. The 4 who have been followed for three months or more showed increase in weight and relief of respiratory symptoms after being placed on the regimen described.

The impression received from these and other cases in which the regimen of diet, high vitamin A intake and administration of pancreatin was followed only in part may be summarized as follows: Administration of pancreatin alone or in combination with vitamin A did not prevent bronchopneumonia (cases 4 and 16). A low fat diet alone permitted the prolonged survival of several patients with late onset of the disease, but the nutrition and the status of the infection of the respiratory tract were improved by institution of the complete regimen. In several cases, however, notably cases 4, 6 and 21, omission of vitamin A therapy was followed by pneumonia. A low fat diet in which vegetables are not included is usually deficient in vitamin A; and even when vegetables are included the carotene is poorly absorbed, as shown by the low serum carotene levels of the patients. On the other hand, a diet

containing a normal proportion of fat results in these cases in retention of vitamin A in the intestine and its consequent loss to the body. It is therefore difficult to evaluate the effect of diet alone as compared with the effect of vitamin A deficiency alone. Together they appear to exert a greater influence than administration of pancreatin.

PHYSICAL STATUS OF SURVIVING PATIENTS IN JANUARY 1945

The health, as well as the survival, of the patient is an objective of therapy. Congenital pancreatic deficiency is a permanent disability, and it is appropriate to consider the degree to which it handicaps the child. All of the surviving patients have a large appetite, must remain on a controlled diet, possess a more or less protuberant abdomen and excrete one or more unusually foul large stools per day. These features may be said to constitute the minimum handicaps, those which are unavoidable even with early diagnosis and what is now regarded as optimal therapy. Further symptoms and handicaps are not uniformly present, even though common. A rough estimate of the present status of the living patients is given in table 4. It may be observed that the patients who have been followed longest are for the most part normally active and without cough. The exceptions are G. D. and R. E. (cases 4 and 9), both of them patients who have been out of range of supervision in recent years and are known to have followed the regimen only intermittently. Some of the others, such as C. J. and V. D. (cases 11 and 22), had a chronic cough for several years, with gradual improvement until at the time of writing they give no evidence of bronchitis. A few years ago, both of these boys showed the barrel chest suggestive of bronchiectasis, but this feature has become less conspicuous, and the contours of the chest approach the normal. Paranasal sinusitis seems to persist longer than chronic bronchitis; it has several times been the presenting symptom.

Moderate retardation in growth is frequently present and is closely correlated with the severity and duration of the infection. It is to be expected that the children who have had chronic infection and consequent slow growth during part of the first two years will be short for their age even after the normal rate of growth is resumed. Most of the children who are doing well are normal in nutrition but undersized; those who have had little or no infection are of normal height. The heights of 16 children are listed in table 4. These figures have been checked against a standard growth chart.[14] One child is in the lowest first, percentile; 7 are in the range of 1 to 25 per cent; 4 are in the range of 25 to 50 per cent, and 4 are above the fiftieth percentile level. The heights of several children with a difficult early course and earlier retardation are now, at the age of 5 or more years, within the median range.

The muscular development and the activity of the children are normal when infection has been absent for some months. There is a close correlation of inactivity, small atrophic muscles and degree and chronicity of infection. The small muscle masses and poor tone are not necessary manifestations of the disease. Rectal prolapse is a common and troublesome complication when nutrition and muscular tone are poor; as these improve, prolapse becomes less frequent and eventually ceases.

As clinical experience with these patients accumulates, one is impressed with the major role played by infection of the respiratory tract, with respect not only to survival but to all the disabilities associated with the disease beyond the "minimal" ones previously listed. Dietary therapy seems capable of preventing special susceptibility to infection, and some patients who remain free from fresh infections over long periods gradually lose the chronic cough. On the whole, dietary therapy has only a moderate effect on well established chronic bronchitis and none on suppurative bronchitis. These conditions must be attacked by other means and will be considered further in a subsequent report.

SOCIAL HANDICAPS OF THE CHILD WHO HAS "DONE WELL"

In evaluating the success of therapy it is relevant to consider the social and emotional effects of the disease and the therapy. Seventeen children are under observation at the time of writing, many of whom have been followed for several years and several of whom are now in school. All of them have been subjected to somewhat abnormal circumstances which may be briefly summarized without attempting an elaborate analysis. Outstanding among these factors is the underlying anxiety which most of the parents feel, especially when they have experienced the illness and death of previous children from the same disease. There is also real need for restricting exposure of the children to infections of the respiratory tract. The tendency is therefore to overprotect the child, keep him in isolation and concentrate the attention of the family on him

14. Holt, L. E., and McIntosh, R.: Holt's Diseases of Infancy and Childhood, ed. 11, New York, D. Appleton-Century Company, Inc., 1940, pp. 14 and 22-25.

o the exclusion of the needs of the rest of the roup. Some of the parents have had the courage nd wisdom to maintain an environment approaching a normal one; but this is not achieved ithout effort, and the emotional burden on parnt and physician is not light.

The children who have a mild chronic cough, s many of them do, become fatigued more uickly than their comrades and are often not up o the average for their age in size and muscular evelopment. When they are free from infection r nearly so (as in cases 11, 13, 21 and 26), here is no such handicap. The dietary limitaions are not severe, and the restrictions are really elt for the first time when lunch at school brings ut contrasts. Difficulty in feeding has been encountered only when the usual hunger was reuced because of severe infection. Most of the hildren accept the supplements without difficulty. After becoming accustomed to pancreatin, they sually desire it, and the flavor is as important part of the meal to them as that of garlic to ome of their elders.

The increasingly improved prognosis has done much to alleviate anxiety. It is now possible to assure the parents that 5 children with the disease are in school and that theoretically there is no reason that they should not continue to improve. If further experience fulfils this hope, it will be possible to view with confidence the future of those patients who have passed the first few years without having bronchiectasis. At present, isolation even from the family group is encouraged through the hazardous first year. After this, it has seemed wiser to risk infections of the respiratory tract in the interest of providing the child with normal human contacts than to handicap him by continued isolation. Patients who have been on the regimen for some time and are well nourished and presumably saturated with vitamins have in fact recovered promptly from fresh infections of the respiratory tract, sometimes with the assistance of chemotherapy.

SUMMARY AND CONCLUSIONS

A dietary regimen has been outlined for treatment of congenital pancreatic deficiency. It consists essentially of a low fat, high protein diet with a liberal allowance of vegetables, fruits and sugar and moderate restriction of starch. Supplements of vitamin A are essential, and pancreatin and vitamin B complex are given.

Evaluation of the success of dietary therapy is difficult because of the wide variation in developmental retardation, severity of infection and period of survival of both untreated and treated patients. An attempt has been made to classify the cases on the basis of clinical criteria instead of age at death, as was previously suggested. The criteria used are the age at which the cough first appears and the gain in weight during the first month of life. Cases of early onset are defined as those in which the cough appears before the age of 6 months. There is a correlation of the rate of gain during the first month, the age of first cough and the period of survival with or without therapy.

Comparison of the periods of survival of treated and untreated patients demonstrates that treatment prolongs survival in cases both of early and of late onset. Of 20 untreated patients with early onset, only 2, or 10 per cent, survived the first year, and none of these survived the fifth year. Of 26 patients with early onset in the present series, 14, or 54 per cent, survived the first year and 3, or 11.5 per cent, the fifth year; 8 of them are living, 2 of these having passed the fifth year. Of 16 untreated patients with late onset, 10, or 62.5 per cent, survived the first year and 2, or 12.5 per cent, the fifth year. In the treated series, all of the 12 patients with late onset survived the first year, and 9 are living, 6 of them over the age of 5 years. The prognosis is therefore better for patients with late onset and for patients receiving treatment. Seventeen, or 43.7 per cent, of the 38 patients of the treated series are living, at ages of from 1 to 12 years.

The effectiveness of the regimen is dependent on the degree and type of infection of the respiratory tract present when dietary treatment is begun. When it is begun prior to the appearance of the cough or immediately after it, the result has been normal growth and development. When it is begun after a chronic cough has been present for some time but before appearance of suppurative bronchitis, the usual result is prolonged survival, with gradual improvement in the cough. When it is begun after onset of suppurative bronchitis, it may prolong life somewhat but will not alter the bad prognosis.

When the regimen has been relaxed for several months, further infection of the respiratory tract has followed. It appears probable that dietary therapy should be continued throughout life.

The parental anxiety and the necessity of reducing exposure to infections of the respiratory tract tend to lead to overprotection and isolation of the child. Emotional factors are an important part of the therapeutic problem and should be considered in the practical management of these patients. Little difficulty has been encountered in carrying out the dietary regimen.

Broadway and One Hundred and Sixty-Seventh Street.

Case Reports

PSEUDOSCLEROSIS

M. G. PETERMAN, M.D.
MILWAUKEE

This case of pseudosclerosis is reported because there seems to be considerable confusion in the literature concerning pseudosclerosis, Wilson's disease (progressive lenticular degeneration) and similar conditions. The history and the physical examination in this case reveal such close conformity to the disease entity of pseudosclerosis as described by Westphal [1] and Strümpell [2] and the disease is so extremely rare [3] that this case is considered of great interest.

REPORT OF A CASE

History.—G. S., a 14½ year old girl, was brought to my office on March 24, 1945. Early in 1944 her teacher reported a weakness of the child's right hand. During the summer the child's speech became thicker and she complained frequently of headaches. In Setpember 1944 a staggering gait and jerky movements of the extremities developed. A roentgenogram of the skull was taken at that time and was reported to show no abnormality. A diagnosis of Sydenham's chorea was made elsewhere. In November 1944 the child had a jacksonian convulsion, which involved the right arm and the right side of the face. She was hospitalized for two weeks and treated with phenobarbital. In January 1945 a second convulsion occurred, which involved the entire right side of the body and continued for ten days while she was in the hospital. Since that time the child had laughed aloud frequently for no apparent reason. She had a constant grin. She was unable to walk without support. The mental deterioration had been rapid, from alertness and intelligence to idiocy. Since January 1945 the child had been given diphenylhydantoin sodium, 0.032 Gm. five times a day, and phenobarbital, 0.032 Gm. three times a day.

Physical Examination.—Physical examination showed generalized muscular rigidity, coarse tremor and ataxia. The mental response was very slow. There were spastic dysarthria and some dysphagia. There were carie teeth and spongy gums. The child was subject to i voluntary laughter.

She was admitted to Milwaukee Children's Hospit March 24, 1945. She would usually sit in bed in posture suggestive of extreme fatigue, a constant sil grin on her face (fig. 1). Her posture is well illus trated in the figure. She was content to sit all da and watch the activity in the ward. There was al some tendency to catatonia. This is also illustrated i the figure. The striking finding, of course, was the gree ish brown ring around the edge of the cornea, de scribed by Westphal and Strümpell. There were n signs of involvement of the pyramidal tract; there wa no nystagmus, no atrophy of the optic nerve and n oculomotor palsies.

Laboratory Data.—The urine was normal with nor mal urobilin content. The spinal fluid showed 1 cell pe cubic millimeter, 30 mg. of protein and 52 mg. of suga per hundred cubic millimeters, and a colloidal gold curv of 0123210000. The Wassermann test gave a negativ reaction, as did the Kline precipitation test for syphili and the van den Bergh test. The prothrombin tim was normal. The liver was not enlarged, and there wa no evidence of pathologic change in this organ.

Course.—On May 10 the father, in a report, state that the child had had several spasms of the face, whic lasted over a week. They were not so severe as the had been previously. The child had been in bed unti the preceding four days and since that time had bee up and around the house. She still could not use he right hand but had a good appetite and was muc stronger.

CONCLUSIONS

In the case of pseudosclerosis (Strümpell-Westphal pseudosclerosis) reported here the physical findings were typical of those described by these authors. This disease is much more rare than progressive lenticular degeneration and is distinctive, with convulsive attacks, rapidly progressing dementia and no involvement of the pyramidal tract. Up to the time of writing, the patient has shown no evidence of hepatic disease. The brownish green ring around the cornea, the facies and the catatonia are present as illustrated in the accompanying photographs.

411 East Mason Street.

1. Westphal, C.: Arch. f. Psychiat. **14**:87, 1883.

2. Strümpell, A.: Deutsche Ztschr. f. Nervenh. **12**: 115, 1898; **14**:398, 1899.

3. Curran, F. J.: J. Neurol. & Psychopath. **12**:326 (April) 1932. Babcock, C. G., and Brosin, H. W.: Hepatolenticular Degeneration, Arch. Neurol. & Psychiat. **46**:431 (Sept.) 1941. Glazebrook, A. J.: Edinburgh M. J. **52**:83, 1945.

The illustration shows the characteristic vacant expression of G. S., a 14½ year old girl with pseudosclerosis; her typical posture and an eye showing greenish brown ring around edge of cornea.

CONGENITAL ESSENTIAL THROMBOPENIC PURPURA

REPORT OF A CASE AND REVIEW OF THE LITERATURE

MAURICE MORRISON, M.D., AND A. A. SAMWICK, M.D.
BROOKLYN

As a preliminary to reporting this case of ngenital thrombopenic purpura, it seemed per-nent to review the literature in order to deter-ine whether the criteria for a correct diagnosis d been fulfilled in every instance of so-called ngenital thrombopenic purpura. Perusal of e literature revealed the fact that thirteen servers had reported cases of this disease. hese cases were scrutinized carefully, observing e criteria which will be noted here.

Since the advent of new procedures, in the st decade, finer methods of study in the hemor-agic tendencies have been utilized. These clude study of the megakaryocytes in the bone arrow and estimation of the prothrombin level. all fairness to previous reports, diagnosis made authors without benefit of bone marrow and rothrombin determinations have been accepted the rest of the findings made the diagnosis ausible. In the future, however, much can gained by adhering to the criteria to be out-ned here.

CRITERIA FOR A DIAGNOSIS OF THROMBOPENIC PURPURA

Characteristics of the Disease.—A proved case thrombopenic purpura (essential) should ow the following features:

1. Purpura, with petechiae and ecchymoses
2. Increase in bleeding time
3. Increase in clot retraction time
4. Decrease in platelets
5. No change in coagulation time
6. No change in prothrombin time
7. Either normal or increased number of megakaryocytes and/or immature megakaryocytes
8. Normal vitamin C content
9. Positive response to tourniquet test
10. Normal or slightly enlarged spleen
11. Absence of adenopathy
12. Leukemoid reaction with leukocytosis and polynucleosis, especially in the presence of active bleeding
13. Absence of lymphocytosis, especially in the presence of active bleeding
14. Absence of leukopenia

The diagnosis of congenital thrombopenic purpura is predicated on presence of these findings at or before birth.

Differential Diagnosis.—In making the diagnosis of essential thrombopenic purpura one must be careful to exclude the following conditions:

1. Acute or chronic leukemia. Leukemia, especially the acute type, most frequently comes up for consideration because of the pronounced thrombopenia. Abnormal cells in the peripheral smear and a myeloblastic marrow readily reveal the true condition.

2. Scurvy. This condition may be present with or without thrombopenia and a low ascorbic acid level, but in cases of scurvy one will note an almost miraculous response to ascorbic acid therapy. The coagulation time is normal; the prothrombin time is within normal limits.

3. Telangiectasia and/or angioasthenia. With these conditions one notes fine capillary formation over the skin covering the orbit, the alae nasi and the buccal mucosa. Especially prominent is the "buccal caput medusae," which presents itself as a serpentine configuration of the capillaries spreading over in juxtaposition to the molar area. One notes also the simple, spiderweb variety of nevi over the skin of the chest and back and over the extremities. Furthermore, one notes varicosities of the lower extremities and the presence of hemorrhoids. Any one of these findings may be familial. These conditions may be associated with splenomegaly and/or hepatomegaly. The response to the tourniquet test is usually positive. At times there are episodes of so-called idiopathic subarachnoid hemorrhages and of hemorrhages into the vitreous or into the kidney (the renal hemophilia of Senator). The bleeding and coagulation times are normal. The prothrombin and vitamin C levels are within normal limits.

4. Allergic purpura. This disease is associated with other manifestations of allergy, such as urticaria and eosinophilia. The platelets are normal in number. The bleeding, coagulation and clot retraction times are within normal limits.

5. Schönlein's purpura (nonthrombopenic purpura of unknown cause). A patient with this condition shows evidence of purpura about the joints, sometimes simulating rheumatic fever. The platelets are within normal limits. All other hemorrhagic criteria are normal. The response to the tourniquet test is usually negative.

6. Henoch's purpura. This disease is associated with abdominal manifestations and usually with cramps and melena. Otherwise the findings are like those of Schönlein's purpura.

7. Hemophilia. The bleeding and clot retraction times are within normal limits. The coagulation time is prolonged. The prothrombin and vitamin C levels are within normal limits. The family history is diagnostic.

8. Static purpura. This disease involves the lower extremities of persons who stand a great deal (e. g., salespeople). It is probably one of the phases of telangiectasia.

9. Toxic purpura. This disease is frequently observed in patients with septic states or febrile conditions. The bleeding and coagulation times and the prothrombin and vitamin C levels are within normal limits.

The diagnosis of essential thrombopenic purpura will rest on solid ground if these considerations are kept in mind. This principle was observed in analyzing both our own case and the cases reported in the literature.

REVIEW OF THE LITERATURE

The patient in Greenwald and Sherman's case had a bleeding time of five minutes and a coagulation time of thirty-five minutes. There was no clot retraction in twenty-four hours. The patient undoubtedly showed a hemorrhagic tendency. No prothrombin studies were done. At autopsy megakaryocytes were scarce in the bone marrow. This reduction is contrary to present observations regarding thrombopenic purpura. This case does not satisfy the criteria for the diagnosis.

In the case of Sanford, Leslie and Crane the bleeding time was normal during the period of thrombopenia; thus essential thrombopenic purpura is ruled out. In the case of Davidson

TABLE 1.—*Summary of Cases in Which a Diagnosis of Congenital Thrompopenic Purpura Hemorrhagica Was Made*

Author	Year	Family History	Sex	Purpura	Platelets	Bleeding Time	Coagulation Time	Clot Retraction	Comment
Dohrn [10].....	1873	Mother cachectic							
Hanot and Luzet [9]	1890	Mother had streptococcic septicemia	..	.....	.....	.....	.....	.....	Meningitis transmitted to child
Zangemeister [11]	1898	Mother had purpura and bleeding gums	..	.....	.....	.....	.....	.....	Fetus dead, with purpuric spots
Mosher [7].....	1923	Mother had purpura	F	Ecchymoses when touched	.....	.....	.....	.....	Toxemia
Waltner [13].....	1924	Mother had 60,000 platelets and purpura	F	3+	90,000	12 min.	10 min.	None	Congenital purpura
Rushmore [6].....	1925	Mother had itching and purpura	..	.....	.....	.....	.....	.....	Miscarriage, with dead fetus
Liebling [5].....	1926	Mother had 40,000 platelets then 300,000 platelets	F	2+	40,000; then 240,000	Normal	Normal	.....	Symptomatic purpura
Greenwald and Sherman [1]	1929	.....	M	3+	30,000	5 min.	35 min.	None	Necropsy—few megakaryocytes
Conti [3].....	1933	Mother had purpura	..	.....	.....	.....	.....	.....	Dead fetus, with bloody spinal fluid
Siegler [12].....	1934	Mother had toxic purpura	..	.....	.....	.....	.....	.....	Baby dead at 4 days; toxemia
Sanford, Leslie and Crane [2]	1936	Mother had purpura and 10,000 platelets	F	Rash with 2+	20,000; then 137,000	.....	Normal	.....	Increased disintegrative platelets
Davidson [3].....	1937	Mother had splenectomy for purpura	F	3+	30,000; then 672,000	Normal	Normal	None; then normal	Tourniquet test—3+
Whitney and Barritt [4]	1942	Mother had splenectomy for purpura	1. M	None	70,000	1 min.	3 min.	None	Enough megakaryocytes
			2. M	2+	90,000; then 113,000	11 min.; then normal	Normal	Not done	Intracranial hemorrhage

1. Greenwald, H. M., and Sherman, I.: Congenital Essential Thrombocytopenia, Am. J. Dis. Child. **38**: 1245 (Dec.) 1929.

2. Sanford, H. N.; Leslie, E. I., and Crane, M. M.: Congenital Thrombocytopenia, Am. J. Dis. Child. **51**: 1114 (May) 1936.

3. Davidson, L. T.: Congenital Thrombopenia, Am. J. Dis. Child. **54**:1324 (Dec.) 1937.

re were plenty of platelets, and therefore this e does not fall within the scope of this study. the cases of Whitney and Barritt [4] the study s not adequate to justify a diagnosis of essen- l thrombopenic purpura. The bleeding time s at all times within normal limits; the clot raction time was never determined. There s a low prothrombin level indicative probably hypoprothrombinemia and subsequent cerebral morrhage.

In Liebling's [5] case thrombopenia was present, t the bleeding time was normal. The clot raction time was not determined. Prothrom- n studies were not being done at that time. e platelet count rose later to 240,000 per cubic llimeter, without any treatment. This case y have been one of symptomatic purpura. Rushmore's case [6] was that of a dead fetus. ere was no hematologic investigation. The no study. Zangemeister's case,[11] in 1898, involved a dead fetus, which presented purpura. The mother had purpura and bleeding gums. There was no hematologic study. In Siegler's case [12] purpura occurred, in a baby 4 days old. There was no hematologic investigation.

In the case reported by Waltner [13] there were 90,000 platelets per cubic millimeter, with an increase in bleeding time; the clot retraction time was not determined. One may assume, however, that this was a true case of essential thrombopenia associated with severe purpura, in spite of the meager hematologic studies which could be made at that time.

REPORT OF CASE

The following case is reported because the disease is congenital and at the same time presents the criteria necessary for a diagnosis. Ade-

TABLE 2.—*Peripheral Blood Findings for S. D's Family* *

tient	Date	Hemoglobin, %	Red Cells per Cu. Mm.	White Cells per Cu. Mm.	P	Eos.	St	B	L	M	Platelets
	5/18	97	.....	.....	..	..	..	..	..	..	Very few
	5/19	81	4,000,000	15,500	42	3	3	1	48	3	1+
	5/20	85	3,900,000	13,800	35	6	1	1	54	3	1+
ther.....	....	..	.....	.....	52	4	..	..	40	4	2+
ther.....	....	..	.....	.....	52	..	..	..	44	4	4+

* In this table, and in table 3, P indicates polymorphonuclear leukocytes; Eos., eosinophils; St, staff forms; B, basophils; L, phocytes, and M, monocytes.

TABLE 3.—*Elements of Bone Marrow of Patient S. D.**

Date	Myc	E Myc	Meta	St	P	Eos.	G : E	E : N	G : P	My : L
5/22	45	0	15	15	15	5	85 : 15	20 : 80	85 : 15	70 : 30

* In this table, in addition to the abbreviations noted in table 2, the following designations are used: Myc, myelocytes; E Myc, inophilic myelocytes; Meta, metamyelocytes; G : E, granulocyte-erythroblast cell ratio; E : N, erythroblast-normoblast io; G : P, granulocyte-polymorphonuclear leukocyte ratio, and My : L, myeloid-lymphoid cell ratio (Morrison, M., and Sam- k, A. A.: Am. J. M. Sc. **198**: 758, 1939).

me statement may be made of the cases re- rted by Mosher [7] and Conti.[8] Hanot and uzet's case [9] involved toxic purpura following eningitis, which was transmitted from mother fetus. The case of Dohrn,[10] in 1873, had quate attention has been given to ruling out the other conditions that come up for consideration in the differential diagnosis of essential thrombopenia.

S. D., a white boy, was admitted to the Jewish Hospital of Brooklyn at 16 days of age, on May 18, 1942. There was a history of purpura and rectal bleeding since his birth, on May 2, 1942, at the South Nassau Communities Hospital. The baby was born at term and delivered spontaneously; his weight was 6 pounds 8 ounces (2,948 Gm.). Eight hours after his birth purpuric spots were noted on the baby's skin. Blood studies made at this time revealed a platelet count of 40,000 per cubic millimeter. Blood studies of the mother

4. Whitney, L. H., and Barritt, A. S., Jr.: Spon- neous and Hereditary Thrombopenic Purpura in a other and Two Sons, Am. J. Dis. Child. **64**:705 (Oct.) 42.

5. Liebling, P.: Purpura Hemorrhagica Complicat- g Pregnancy, Am. J. Obst. & Gynec. **11**:847, 1926.

6. Rushmore, S.: Purpura Complicating Pregnancy, n. J. Obst. & Gynec. **40**:553, 1925.

7. Mosher, G. C.: The Complication of Purpura th Gestation, Surg., Gynec. & Obst. **36**:502, 1923.

8. Conti, F.: Diatesi emorrhagica con ultimo epi- dio in gravidanza e con manifestazioni fetali, Rassegna ernaz. di clin. e terap. **14**:450, 1933.

9. Hanot, V., and Luzet, C.: Note sur le purpura streptocoques, Arch. de méd. exper. **2**:772, 1890.

10. Dohrn: Ein Fall von Morbus maculosus Werlhofi ertragen von der Mutter auf die Frucht, Arch. f. näk. **6**:486, 1873.

11. Zangemeister: Komplikation von Schwangerschaft und Geburt mit hämorrhagischer Erkrankung, Ztschr. f. Geburtsh. u. Gynäk. **39**:593, 1898.

12. Siegler, S. L.: Purpura Hemorrhagica Complicating Pregnancy, M. Rec. **139**:189, 1934.

13. Waltner, K.: Ein Fall mit angeborenen manifesten Symptomen des Morbus Werlhofi, Jahrb. f. Kinderh. **106**:307, 1924.

showed that her platelet count had also diminished to 40,000.

Rectal bleeding was noted during the first few days, and on the sixth day bloody sputum was obtained. On the ninth day the platelets increased to 70,000, and the purpura began to disappear. Three days prior to his admission to the hospital rectal bleeding was noted again, and it continued to the day of his admission.

The mother and the mother's sister bruised easily. The mother was a secundigravida and primipara. The first pregnancy ended in spontaneous abortion at two months.

Examination revealed that the baby was slightly thin but well developed. He had a lusty cry and did not appear acutely ill. The respirations were normal. The positive findings were as follows: There were petechiae on the hard palate; there was some clotted blood at the umbilicus; the spleen was not felt, and the liver was palpable 1 fingerbreadth below the costal margin.

Hematologically (table 2) one noted definite thrombopenia associated with giant platelets, lymphocytosis and some eosinophils. There was no significant petechiasis at this time. No immature cells were noted.

On May 20 the patient showed no further evidence of bleeding, but there were clusters of petechiae in both femoral folds. The spleen was not palpable. Aspiration of the bone marrow (table 3) showed an increase of megakaryocytes. The platelets were still diminished. There was no evidence of erythroblastosis in the bone marrow. The lymphocytes were increased, and there was a left shift of the myeloid white elements. The bleeding time was seven to eight minutes. The coagulation time was three and one-half minutes. The prothrombin time was within normal limits. There was no clot retraction in thirty hours.

On May 21 there were no external evidences of bleeding, but the stools showed evidences of blood.

Blood studies on the mother revealed a normal differential count, with 4 eosinophils, but there were a definitely diminished number of platelets and a number of giant platelets. There were no abnormal findings in the father's peripheral blood.

COMMENT

In reporting a case of congenital and/or essential thrombopenic purpura one must be sure about two features: First, the disease must be congenital, and, second, the purpura must be essential, or idiopathic. If all the conditions capable of producing thrombopenic purpura have been ruled out and if other conditions capable of producing hemorrhagic diathesis have been considered, there still remain criteria which are pathognomonic. These are: (1) increased bleeding time; (2) diminished platelets; (3) megakaryocytes—normal or increased in number; (4) poor clot retraction; (5) normal coagulation time; (6) normal prothrombin time, and (7) normal vitamin C level.

SUMMARY

In a case of congenital essential thrombopenic purpura the mother and the maternal grandmother showed evidence of purpura, with a tendency to thrombopenia.

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135 Eastern Parkway.

Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

BIOASSAYS OF UTILIZATION OF CALCIUM IN BRAZILIAN VEGETABLES: I. AMARANTHUS FLAVUS. D. COSTA and E. TÁCCOLA, Med. cir. pharm., November 1943, p. 619.

The authors refer, first, to the importance of calcium deficiency in the general malnutrition of the Brazilian population. Lack of calcium and iron, of the mineral elements, constitutes the most serious dietetic problem of Brazil. Relative importance must be given to the total calcium content of several foods, it being more important to regulate the rate of utilization of calcium in the various foods.

In experiments on two groups of rats of the same age, calcium metabolism was regulated for each group, after thirty-five days of observation, during which the animals were fed different diets: In one of the diets, all the calcium was derived from milk; in the other, the same quantity of calcium was furnished, in the ratio of 1:1, by a mixture of milk and carurú (Amaranthus flavus).

The rate of utilization of calcium in the milk was 0.65 and that in the carurú-milk mixture, 0.45.

The high content (about 1 per cent) of oxalic acid in the vegetable in question was also verified. Carurú (Amaranthus flavus) has a high calcium content, 0.538 gm. per cent, of the edible portion.

AUTHORS' SUMMARY.

NATURAL ENRICHMENT OF BREAD WITH POWDERED MILK. HÉLION PÓVOA and D. COSTA, Resenha clin.-cient. **12**:381 (Oct. 1) 1943.

In order to obtain a new process of natural enrichment of bread, in view of the well known deficiencies of white bread, the authors studied a new mixture containing three elements: white flour (72 per cent of extraction), whole wheat flour and powdered skim milk. All the researches were carried out through S. A. S. (Servico de Alimentacão da Previdência Social), an official institution of the Brazilian government, which possesses, among others, the functions of an organ of investigation of new sources of foods and of determination of the nutritive value of Brazilian foodstuffs.

This bread has the following advantages over the common white bread: more than three times the calcium content, almost three times the phosphorus content and twice the iron content.

Comparison of 30 Gm. of white bread, made with water, and 30 Gm. of the "three mixture bread" reveals the following differences, which suffice to indicate the good results of the proposed method:

	Calcium, Gm.	Phosphorus, Gm.	Iron, Gm.
White bread	0.008	0.029	0.0002
"Three mixture bread"	0.027	0.067	0.0005

The authors made the "three mixture bread" according to the following formula:

White flour	73%
Whole wheat flour.....	25%
Powdered skim milk.....	2%
Water	q. s.
Yeast	q. s.

The authors obtained, besides the advantages already established, a bread of lower acidity than that of common bread.

AUTHORS' SUMMARY.

Hygiene; Growth and Nutrition; Public Health

CHILD PROTECTION AND THE INTERNATIONAL LABOR CONFERENCE AT PHILADELPHIA. RUDOLF ALADÁR MÉTALL, Bol. Inst. internac. am. de protec. a la infancia **18**:626 (Dec.) 1944.

In this article, the author summarizes the decisions made by the twenty-sixth session of the International Labor Conference relative to child protection. The "Philadelphia Charter" and the various recommendations adopted in May 1944 refer, among other things, to some problems of protection of childhood and youth. Recommendations 67 on income security, 69 on medical care, 71 on employment (transition from war to peace) and 70 on social policy in dependent territories contain dispositions relative to adequate and efficient protection of children, especially those of the laboring classes. The article systematically summarizes these dispositions, which show the preoccupation of the International Labor Organization with the physical and intellectual welfare of today's children, who are tomorrow to be the free men of a better world.

EDITOR'S SUMMARY.

Prematurity and Congenital Deformities

CONGENITAL MALFORMATIONS INDUCED BY MATERNAL NUTRITIONAL DEFICIENCY. JOSEF WARKANY, J. Pediat. **25**:476 (Dec.) 1944.

Three examples of experimental production of congenital malformations in rats by maternal nutritional deficiency are presented.

By breeding mother rats which were receiving a diet free of carotene and vitamin A, offspring were obtained which showed congenital malformations of the eyes, such as fusion of the cornea and the lids, absence of the anterior chamber, of the iris and of the ciliary body, coloboma retinae and a membrane of embryonic connective tissue in place of the vitreous.

On a diet deficient in riboflavin, female rats produced offspring one third of which showed congenital skeletal defects. These defects consisted of shortness of the mandible and of the tibia, fibula, radius and ulna; fusion of ribs and of fingers and toes, and a cleft palate. This pattern of malformations could be prevented by the addition of liver or of crystalline riboflavin to the maternal diet.

With a maternal diet high in calcium, low in phosphorus and lacking vitamin D, another type of skeletal malformations could be obtained. There was curving of the radius, ulna, tibia and fibula, as well as abnormal angulation of the upper ribs. Malformations of this type could be prevented by a supplement of vitamin D to the maternal diet.

WARKANY, Cincinnati.

Newborn

NASAL INJURIES IN DYSTOCIA. MATTHEW S. ERSNER, Ann. Otol., Rhin. & Laryng. **53**:552 (Sept.) 1944.

Ersner discusses a situation which has been present since births began but which has only recently been recognized as a definite factor in the development of septal deflections and nasal obstruction. He points out that during the birth of a child a tremendous pressure (up to 30 or 40 pounds [13.5 or 18 Kg.]) is exerted by uterine contractures on the child, forcing it down through the pelvis. With Dr. N. Kendall, of Temple University Hospital, in studies of measurements of 25 newborn infants, he found that there was a variation of from 1 to 2.5 cm. of outward projection of the nose. In only 1 child, a Negro, was there an exception, and here the occipitofrontal and occipitonasal measurements were the same. With a so pronounced projection the nose is bound to receive considerable trauma in passing through the birth canal with such great pressure behind it, and this trauma is increased in dystocia with a large head in relation to the pelvis. The most common injury to the nose as a result is a dislocation of the cartilaginous portion of the septum from the vomeric groove. Rarely does the obstetrician look for intranasal injury, and such injury is thought of only after it is noted that the child has difficulty in nursing, as well as in breathing through the nose. Ersner feels that every obstetrician should routinely inspect the infant's nose for septal deflections or anatomic dislocations and fractures of the nose, just as routine examinations are conducted to determine the presence of any other deformities or injuries. It is best to correct the deformity immediately before a greenstick fracture results or a callus forms. Reduction is readily done by grasping the tip of the nose and gently but firmly pulling from side to side or by tugging the tip of the nose slightly ventrally. Usually one can feel the cartilage slip into place on the vomer. In more difficult cases instruments may be used to grasp the cartilage. If a fracture or dislocation is neglected or overlooked and there is a lapse of several weeks, the additional problem of callus develops. If the condition is entirely overlooked, one may find in later life a deflected septum and nasal obstruction, trigger points with resultant reflex nerve involvement, faulty development of the upper jaw, sinusitis or the so-called adenoid facies, due to nasal obstruction, and last, but not least, the whole background becoming a panorama of "noseology" at adolescence. As the nose begins to grow, the external deformity becomes apparent by distortion, asymmetry, concavity or hump.

MILLER, Philadelphia. [ARCH. OTOLARYNG.]

ALTERATIONS IN BRAIN STRUCTURE AFTER ASPHYXIATION AT BIRTH: AN EXPERIMENTAL STUDY IN THE GUINEA PIG. W. F. WINDLE, R. F. BECKER and ARTHUR WEIL, J. Neuropath. & Exper. Neurol. **3**:224 (July) 1944.

Windle, Becker and Weil report observations on the effect of asphyxia in guinea pigs. Proof that asphyxia leads to neurologic defects may never be found in the human newborn infant, because adequately controlled conditions—multiple births—are uncommon. These animal experiments supplement clinical observations.

The experimental procedure in most instances was as follows: pregnant guinea pigs at or close to term were operated on after the abdomen was anesthetized with a 1 per cent solution of procaine hydrochloride. One fetus of each litter was delivered without delay to serve as the control for the fetuses to be asphyxiated. The uterine blood vessels or the umbilical cord was then occluded with clamps to induce a state of hypoxia in the remaining fetuses. Violent movements, including respiratory activities in utero, were executed during the first stage of asphyxia. When their respiratory efforts ceased, the fetuses were delivered. The average duration of asphyxiation was a little over thirteen minutes (range, four and a half to twenty-one minutes). The average time required for resuscitation (with oxygen containing 10 per cent carbon dioxide) was twenty-nine minutes (range, a few seconds to well over an hour) for the 66 animals selected for study. Some litters contained 3 or more animals, and two or more fetuses were asphyxiated; 50 controls were provided. Sixty-six of the newborn guinea pigs were resuscitated and lived thirty minutes to thirteen weeks. The brains of all the animals were preserved and sectioned serially. Observations were made on sections stained by various technics.

Multiple capillary hemorrhages, and occasionally larger hemorrhages, were noted in all animals which survived asphyxiation for three hours to five days. These lesions were observed in half the animals which survived from thirty minutes to two hours, while no lesions were observed in the animals which did not survive the period of asphyxia. There was a notable variation in the amount and distribution of the hemorrhages. However, hemorrhage was not considered the cause of extensive damage to the neurons.

Edema was present in the brains of all but 1 of the animals which survived eight hours to four days after resuscitation. After five days the edema subsided.

Cytologic changes were observed in all the brains of animals killed from one and one-half hours to twenty-one days after resuscitation. The usual sequence of events was clouding of the Nissl granule pattern, beginning one to two hours after resuscitation; swelling of some neurons and shrinkage of others in three hours; loss of stainability with thionine appearing in about five hours; typical chromatolysis, in one or two days; complete lysis of neurons, as early as four days after resuscitation, and hyperchromatic staining, in at least three weeks. Some specimens presented generalized changes throughout most of the brain, while others showed only focal abnormalities. The cerebellum and the corpus striatum were not notably affected, while the thalamus, cerebral cortex, tegmentum and spinal cord were often severely damaged.

Asphyxia induced a transient microglial reaction between two days and three weeks after resuscitation. Thereafter the glia assumed normal proportions.

Generalized or focal atrophy followed the loss of neurons in about two thirds of the severely asphyxiated animals and in one half of the mildly asphyxiated guinea pigs. As late as thirteen weeks after resuscitation neurons in the damaged brains stained darker and were more shrunken than the neurons in the brains of litter mate controls. Areas of partial necrosis occurred in 8 animals. Loss of myelin appeared to be secondary to loss of cells.

The authors conclude that experimental asphyxiation followed by successful resuscitation in guinea pigs at birth produced pathologic changes of variable degrees of severity in all specimens of the brain studied between one and one-half hours and three weeks after birth and detectable permanent anatomic changes in more than one-half the animals allowed to live more than three weeks.

GUTTMAN, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

VIRUS OPHTHALMIA NEONATORUM. A. SORSBY, E. E. HOFFA and E. N. YOUNG, Brit. J. Ophth. **28**:451 (Sept.) 1944.

An account of the inclusion type of ophthalmia neonatorum is given. From a study of 27 cases observed in a series of 269 consecutive cases of ophthalmia neonatorum at White Oak Hospital it is concluded that, apart from a later onset in most but by no means all cases, inclusion blennorrhea has no features which distinguish it from microbial ophthalmia neonatorum, either in course or in response to sulfonamide therapy. In 5 of 26 mothers of infants with inclusion blennorrhea, cervical scrapings showed inclusion bodies.

The article is illustrated.

ZENTMAYER. [ARCH. OPHTH.]

ANTENATAL DIET AND ITS INFLUENCE ON STILLBIRTH AND PREMATURITY. C. S. CAMERON and STANLEY GRAHAM, Glasgow M. J. **24**:1 (July) 1944.

The patients were divided into two groups. One group continued their usual routine, and the other had the diet supervised and explained by a dietitian. They were also given priority allowances of 1 pint (473 cc.) of milk, 2 eggs, extra fruit juice, extra ration of meat and cod liver oil. There were fewer stillbirths, premature births and neonatal deaths in the supervised group, and a higher number of these mothers fed their babies at the breast.

SNELLING, Toronto, Canada.

Acute Contagious Diseases

ACUTE MENINGOCOCCAL ENECPHALOMYELITIS. WILLIAM B. WARTMAN and IRWIN C. HANGER, Am. J. M. Sc. **208**:234 (Aug.) 1944.

The authors report the case of a young soldier who by clinical examination and laboratory tests appeared to have acute meningococcic cerebrospinal meningitis, with deep coma, difficulty in breathing and extreme pulmonary edema. At autopsy, however, he was found to have had acute encephalomyelitis, violent and extensive, with but comparatively little meningitis. The encephalitis was characterized by purpura of the brain and cord and acute necrotizing exudative inflammation but no demyelination. The case is like those described by Banks and McCartney but differs in that the disease did not occur during an epidemic or at a time when meningitis was prevalent.

HENSKE, Omaha.

MUMPS EPIDEMIC IN A SMALL TASK FORCE. HARRY DERMON and ELTON W. LE HEW, Am. J. M. Sc. **208**:240 (Aug.) 1944.

The authors report on an epidemic of mumps in a small task force. The total man days lost by hospitalization in the series of 129 cases was 2,657. This is a large figure, but it is in keeping with previous experience with mumps in the Army. A correlation is evident between inclement weather and crowded living conditions and the incidence of mumps.

Orchitis developed in 35 per cent of the cases of this series. Neither age nor a history of previous gonorrhea appeared to play a part in the incidence of this complication. One case of mumps meningo-encephalitis and 1 of mumps orchitis without parotitis occurred. Leukopenia with a relative lymphocytosis was present in most cases. The urine uniformly was normal.

Treatment was symptomatic, and results were satisfactory. In 8 cases, sulfathiazole was given and seemed not to affect the course of the mumps.

Of 129 cases, 3 are reported in some detail.

HENSKE, Omaha.

GRANULOMA ANNULARE AND MEASLES. NORMAN M. O'FARRELL, Arch. Dermat. & Syph. **50**:434 (Nov.) 1944.

The author reports on 2 children with granuloma annulare, the lesions of which cleared immediately after measles. The lesions in both patients failed to recur after an interval of several weeks.

MCINTOSH, Iowa City.

THE STATUS OF PASSIVE IMMUNIZATION AND TREATMENT IN PERTUSSIS BY THE USE OF HUMAN HYPERIMMUNE SERUM: REPORT OF THE COUNCIL ON PHARMACY AND CHEMISTRY. HARRIET M. FELTON, J. A. M. A. **128**:26 (May 5) 1945.

A review of the literature indicated that human hyperimmune serum will lower the mortality rate and give significant passive protection in cases of pertussis when it is given in the recommended doses. Various methods of preparing the serum are described. The National Institute of Health recognizes no standard method of assay at the present time. The use of lyophiled serum facilitates administration and storage. The use of rabbit immune serum and antitoxin is being investigated.

BAIRD, Wauwatosa, Wis.

THE CENTRAL NERVOUS SYSTEM IN DIPHTHERIA. A. B. BAKER and H. H. NORMAN, J. Nerv. & Ment. Dis. **100**:24 (July) 1944.

From the local lesion the Corynebacterium diphtheriae give off a powerful exotoxin that acts on the heart, kidneys and nervous system. The involvement of the nervous system primarily is a toxic mononeuritis or a mononeuritis multiplex producing motor phenomena of a flaccid type. Involvement of the central nervous system is uncommon, but it may appear in three forms: (*a*) toxic delirium which subsides with recovery from the acute illness, (*b*) active toxic encephalitis and (*c*) hemiplegia due to vascular occlusion. The literature regarding involvement of the central nervous system is reviewed, and a case report submitted.

JAHR, Omaha.

PECULIARITIES OF DIPHTHERIA IN CUBA. DOMINGO GÓMEZ TEJERA, Bol. Soc. cubana de pediat. **15**: 1057 (Dec.) 1943.

In Cuba diphtheria is generally benign, with mild febrile and toxic reactions and, rarely, involvement of the nervous system and the heart. It is seldom of the serious, serum-resistant type. The individual susceptibility seems to be lower than that usual in more temperate climates. The mortality in Habana, as elsewhere, was high (58.3 per hundred thousand in one year) until serotherapy was begun. In 1936 the mortality was 1.95 per hundred thousand. Preparation and use of serum were begun in Habana in 1894. In cases of the severe form, strychnine, ascorbic acid, adrenal cortex extract, transfusions, sulfonamide compounds and specific antiserums against associated organisms are also used. Intubation is preferred to tracheotomy in cases of the laryngeal type. Active immunization has been employed in private practice since 1927 and is systematically practiced in many institutions.

KEITH, Rochester, Minn.

WHOOPING COUGH: A CLINICAL AND PROPHYLACTIC STUDY. ÁNGEL C. ARGUDÍN Y GARCÍA and JOSÉ M. MIR Y DEL JUNCO, Bol. Soc. cubana de pediat. **15:** 1087 (Dec.) 1943.

This article is a review of the history, etiology, epidemiology, diagnosis, complications and treatment of whooping cough. The authors feel that prophylactic vaccination has modified profoundly the virulence and intensity of the disease. It is of interest that vaccination is carried out soon after birth rather than after the child is 6 to 9 months old. The child is vaccinated again at 9 months of age. The material used is a concentrated vaccine prepared from the Bordet bacillus, the doses employed being 0.25, 0.5, 0.75 and 1 cc., given at intervals of three days. When an epidemic occurs, the dose is increased to 0.25, 0.5, 0.75, 1, 1 and 1 cc. given at intervals of forty-eight hours.

KEITH, Rochester, Minn.

Acute Infectious Diseases

MAMMALIAN AND AVIAN "TOXOPLASMA." REGINALD D. MANWELL, FREDERICK COULSTON, ELLEN C. BINCKLEY and VIRGINIA P. JONES, J. Infect. Dis. **76:**1 (Jan.-Feb.) 1945.

Toxoplasma of mammalian (in this case human) origin infects a number of host species, both birds and mammals, with varying manifestations. The infection may be acute or chronic, depending on such factors as species, route of inoculation and number of parasites introduced.

All strains of Toxoplasma probably belong to a single species, Toxoplasma gondi (Nicolle and Manceaux, 1909), and are unaffected by the host.

It is uncertain whether birds are naturally infected with strains of Toxoplasma infective for mammals, though they are highly susceptible to experimental infection.

Avian Toxoplasma is not infective for mammals and is probably of coccidian nature.

The structure of the parasites themselves is more typical of the protozoan cell than of the plant cell. Little, however, is known of the life cycle. Toxoplasma does not bear more than a superficial resemblance to Histoplasma.

The tendency which Toxoplasma exhibits in certain hosts to set up a chronic, symptom-free infection of long duration, with or without an acute primary stage, suggests that such infections may not be uncommon in nature. Hosts reacting in this way may be important as reservoirs of the parasite.

Frogs, previously reported as hosts, are resistant to mammalian toxoplasmosis.

The natural means of transmission remains unknown, but infection can take place through ingestion of flesh containing the parasites, congenitally or by ingestion of the contents of the intestine (and hence, presumably, of freshly passed feces). Mice and canaries, though highly susceptible, do not ordinarily acquire toxoplasmosis from others which have the disease and which are kept in the same cages.

The "x bodies" (*Einschlüsse*) seen in the lungs of the canary, though bearing a close resemblance to Toxoplasma, do not give mouse takes and are therefore probably quite different in nature. Previous infection with these bodies or with the avian type of Toxoplasma does not protect against subsequent infection with the mammalian type of Toxoplasma, nor can the avian type be transmitted to mice.

Toxoplasma of the mammalian type can be grow on chick embryos, as was demonstrated in this stud and in other investigations.

It is possible to preserve this parasite in viable co dition by freezing at low temperatures for at lea limited periods. It is, however, highly delicate an very susceptible to drying and to the action of suc antiseptics as ethyl alcohol (70 per cent) and phen (5 per cent). It will not remain alive in an ordinar refrigerator for more than forty-eight hours.

TOOMEY, Cleveland.

CHANGES ASSOCIATED WITH ACQUIRED IMMUNIT DURING INITIAL INFECTIONS IN SAURIAN MALARI PAUL E. THOMPSON, J. Infect. Dis. **75:**137 (Sept Oct.) 1944.

The course of the infection of Plasmodium floriden has been studied in four and of Plasmodium mexicanu in three species of lizards with respect to the numbe of parasites, number of merozoites per segmented an crisis forms. The infections in the various species o lizards resembled in general the initial malarial infe tions of warm-blooded animals, with a definite pea in numbers, a decline in number of parasites and the host does not die a developed infection. The acu infections in saurian hosts, however, developed an subsided more slowly than most malarial infections i warm-blooded animals.

During the developed infection, crisis forms persiste

TOOMEY, Cleveland.

EFFECTS OF PENICILLIN, CLAVACIN AND STREPTOMYCI UPON TETANUS TOXIN. ERWIN NETER, J. Infec Dis. **76:**20 (Jan.-Feb.) 1945.

Sodium penicillin containing 500 to 5,000 Oxfo units of penicillin per cubic centimeter failed to d crease the toxicity of tetanus or caused only a minim reduction in toxicity.

Two milligrams of clavacin rendered tetanus tox nontoxic for mice; 0.2 mg. caused a slight reductio in toxicity.

Ten injections of streptomycin failed to affect th toxicity of tetanus toxin.

The effects of various antibiotic substances on tetan toxin are discussed.

TOOMEY, Cleveland.

THE TRANSMISSIBILITY OF INFECTIOUS MYXOMATOSI RALPH B. HOULIHAN and GEORGE McL. LAWSO J. Infect. Dis. **76:**40 (Jan.-Feb.) 1945.

In a rabbit heavily infected intradermally wi myxoma virus, the virus did not appear in the blo stream for approximately forty-eight hours. It ha reached a peak of 262,000 infectious units per cub centimeter at the time that generalized symptom appeared.

Virus did not appear in the nasal washings unt seventy-two hours after the intradermal injection. I the early stages of the disease the concentration o virus in nasal washings was considerably lower tha the concentration in the blood. This difference wa less marked in the later stages.

Neither feces, urine nor droplets were infectious.

Intact nasal mucosa was more resistant to the viru than was subdermal tissue.

Mere contact exposure during the early stages o myxomatosis was not effective in spreading the disea Either prolonged contact throughout the course o myxomatosis or contact at a time when the gener

ymptoms were definitely advanced was necessary for s transmission.

TOOMEY, Cleveland.

THE PROPHYLACTIC USE OF SULFANILAMIDE IN CHILDREN WITH INACTIVE RHEUMATIC FEVER. KATHARINE G. DODGE, JANET S. BALDWIN and MORTIMER W. WEBER, J. Pediat. **24**:483 (May) 1944.

A study of the chemoprophylaxis of streptococcic fections of the respiratory tract and relapses of rheuatic fever was carried out at Bellevue Hospital during our seasons. During this period 88 children and dolescents with rheumatic infection, whose ages ranged om 5 to 18 years (64 per cent were under 14), were iven small daily doses of sulfanilamide throughout the ll, winter and spring months, for a total of 181 paent seasons. Most of these children gave histories frequent attacks of acute rheumatic fever and had finite evidence of moderate to severe organic heart isease. All were free from active rheumatic disease at e time of entering the study. During the last three asons of the study, a comparable group of 101 chilen with rheumatic infection were followed as conols, for a total of 138 patient seasons. Sixty-three these children were under observation in a special udy being conducted by Dr. Homer Swift and his sociates at the Hospital of the Rockefeller Institute.

Sulfanilamide was used throughout the study, 1 to Gm. a day being given in divided doses, in an effort maintain a level of the drug of from 1.5 to 3 mg. r hundred cubic centimeters in the blood. The chilen were seen in a special clinic twice a week during e first three weeks, once a week during the subseent three weeks and biweekly thereafter as long as e drug was given. They were watched closely for gns of infection of the respiratory tract, relapses of eumatic fever and drug toxicity.

White blood cell counts and determinations of hemoobin were made at each clinic visit, and frequent red ll counts, urinalyses, cultures of material from the se and throat and determinations of erythrocyte sedientation rates, antistreptolysin titers and levels of lfanilamide in the blood were included in the labratory study.

There were no toxic reactions to the drug of suffient severity to cause permanent discontinuance of the ug, although in several instances its administration as temporarily discontinued because of a transient op in the number of granulocytes. This is in conast to reports of other investigators, who found it cessary to discontinue the drug in about 12 per cent cases. There was no evidence of increased sensivity to or increased toxicity of the drug on its readinistration after intervals of a few days to several onths, nor was there evidence of any change in reacon to the subsequent administration of any of the her sulfonamide drugs for therapeutic purposes.

During the period of the study there were in the ntrol group 54 patients with infections due to group hemolytic streptococci, an incidence of 39 per cent. here were 26 relapses of rheumatic fever (19 definite, ith 2 known deaths and 7 possible deaths), an incience of 18.8 per cent; in 3 children the process reained active throughout the period of observation, d 1 child died of subacute bacterial endocarditis.

In contrast, only 5 infections with the hemolytic reptococcus occurred in the group of children receivg sulfanilamide prophylaxis, an incidence of 2.7 per nt. In 2 children, or in 1.1 per cent of the patient asons of prophylaxis, definite relapses of rheumatic ver occurred while the patient was taking the drug regularly. Two other children with severely damaged hearts died of congestive failure without evidence of streptococcic infection or of active rheumatic disease. Two children with recently active rheumatic fever showed signs of increasing rheumatic activity within two weeks of starting the drug. The remainder of this group of children remained free of streptococcic infection and relapses of rheumatic fever.

It is the opinion of the authors, based on the results of this study and on reports in the literature, that the effectiveness of prophylaxis with the sulfonamide compounds in cases of quiescent rheumatic fever is established and that it should be applied more widely among groups of highly suceptible persons. Indications for the prophylactic use of the drug are considered to be two or more frank attacks of acute rheumatic fever with or without evidence of accompanying acute carditis, or one attack of rheumatic fever associated with recognized cardiac damage. Patients with more advanced heart disease with long histories of repeated attacks of rheumatic fever are also considered as candidates, although equally good results are not to be expected in this group.

Because of the possibility of precipitating a relapse in a patient whose rheumatic infection has been recently active, the patient should be without laboratory or clinical evidence of active rheumatic infection for two to three months before starting the drug.

Although other sulfonamide compounds have not had the long clinical trial that sulfanilamide has had, it is probable that sulfadiazine would be equally effective and could be given in one daily dose of 0.5 Gm. for children and 1 Gm. for adolescents and adults.

Careful clinical supervision can probably be substituted for much of the routine laboratory work thought necessary to safeguard the administration of the drug during the experimental stages, although frequent check on the total granulocyte count during the first six weeks is wise.

DODGE, New York.

THE PHARMACOLOGICAL BASIS FOR THE RATIONAL USE OF ATABRINE [QUINACRINE HYDROCHLORIDE] IN THE TREATMENT OF MALARIA. JAMES A. SHANNON, DAVID P. EARLE JR., BERNARD B. BRODIE, JOHN V. TAGGART and ROBERT W. BERLINER, J. Pharmacol. & Exper. Therap. **81**:307 (Aug.) 1944.

This excellent article is too long and too detailed to be abstracted in full. After a single slow intravenous injection of quinacrine hydrochloride and after fourteen daily similar injections into dogs, the higher concentrations of the drug were found in the liver, spleen and lungs, and there was a considerable and progressive storage in these organs. After the repeated injections, the urinary and fecal excretion was slow. In human beings given quinacrine hydrochloride biweekly, there was a progressive increase of the drug in the blood plasma for several weeks, and the rate of fall of the plasma level subsequent to attaining the maximal level was rather low.

These results indicate that administration of the drug several weeks before the person enters a hyperendemic malarial area or the use of large doses shortly before or after exposure would be efficacious in preventing or rapidly curing an infection. In a series of patients the oral, intramuscular and intravenous routes of administration were studied. The intramuscular route for a short time, until the oral route is possible, would seem valuable. However, extended use of the parenteral route is rarely warranted.

PILCHER, Cleveland.

VARICELLA AND HERPES ZOSTER IN SAME PATIENT. F. M. B. ALLEN, Brit. M. J. **2**:115 (July 22) 1944.

It is unusual to encounter the characteristic eruptions of chickenpox and herpes in the same patient. The patient was a 5½ year old boy, an only child, sensitive, highstrung and precocious. He was allergic to pollens and mixed inhalants. His father had a history of allergies. Typical chickenpox developed in the child. Three and one-half weeks later there was an eruption of herpetic vesicles on the right side, extending from the clavicle and deltoid area over the chest and abdomen to the upper half of the right thigh. The eruption was limited by the midline in front and by the midaxillary line. Five days later he had a fever which lasted for two days, with the temperature as high as 104 F.

BIRDSONG, University, Va.

UNUSUAL INFECTIONS WITH THE NEISSERIA. J. ARMYTAGE, M. J. Australia **2**:360 (Sept. 30) 1944.

The author briefly reports a case of gonococcic meningitis, a case of meningococcic vulvovaginitis and 3 cases of meningococcic conjunctivitis and discusses the possible significance of this interchange of habitat between the gonococci and meningococci.

GONCE, Madison, Wis.

EOSINOPHILIA IN OXYURIASIS. A. COSTA and M. COPPO, Rev. chileña. de pediat. **15**:562 (July) 1944.

The authors studied 332 children of both sexes: 254 healthy children, from 6 to 12 years of age, and 76, from 2 to twelve years old, with various infections. In the latter patients Oxyuris was demonstrated by NIH swab; Ascaris lumbricoides and Trichuris trichiura were also searched for. An elevation of eosinophils ranging from 5 to 25 per cent was observed in 55.9 per cent of the entire series—in 56.5 per cent of the clinically healthy children and in 52.7 per cent of the hospitalized group. The average eosinophil count in the former series was 7.1 per cent; in the latter, 9.9 per cent. Eosinophilia was observed in 55.3 per cent of the children with Oxyuris infection alone and in 63.1 per cent of those with mixed types of infection.

PLATOU, New Orleans.

Chronic Infectious Diseases

THE IMPORTANCE OF PRIMARY PULMONARY TUBERCULOSIS. J. V. HURFORD, Proc. Roy. Soc. Med. **37**:585 (Aug.) 1944.

Many complications of pulmonary tuberculosis in children may be prevented if after the primary infection has been incurred they are given a period of rest in bed in an institution, followed by graduated exercise with eventual discharge to their homes or to an open air school.

Hematogenous spread or meningitis are most to be feared within three or four months of infection or longer. Atelectasis occurs more often in children under 5 years and bronchiectasis in the younger age group. Pleural effusion is often interlobar and may come at any time after the first infection (as may an osseous or articular complication). Complete calcification is no criterion of healing. It is possible to have tubercle bacilli in gastric washings though calcification is proceeding in mediastinal glands. The author gives histories of 4 unusual cases and reproductions of the roentgenograms of the same patients.

In conclusion he states that there are drawbacks to hospitalizing the children, such as cross infection, interruption of normal schooling and prolonged stay of th children in hospital in the formative years.

WILLIAMSON, New Orleans.

BRONCHIAL OBSTRUCTIONS IN PRIMARY PULMONA TUBERCULOSIS. W. F. RICHARDS, Proc. Roy. So Med. **37**:589 (Aug.) 1944.

The author in his summary states that bronchi obstruction is a common complication of primary pu monary tuberculosis, especially in children under years old. In the majority it is caused by pressu on a bronchus from an enlarged lymph gland. B obstruction caused by bronchial tuberculosis is n uncommon in children.

WILLIAMSON, New Orleans.

MILIARY TUBERCULOSIS IN INFANCY. CARLOS HE NÁNDEZ MIYARES, JULIÁN ARAÑA FLORIDA a JOSÉ RODRÍGUEZ BETANCOURT, Bol. Soc. cubana pediat. **15**:973 (Dec.) 1943.

The authors present a complete review of miliar tuberculosis in infancy, especially the pulmona varieties. They discuss the difference between s called bacillemia and true tuberculous septicemia; th also discuss the factors which result, on the one han in hyperacute septicemia and a fatal picture and, on th other, in disseminated and nodular, or even innocuou lesions. They feel that in most cases the primary lesio is in the pulmonary parenchyma, the organisms bein carried from the tracheobronchial glands into the bloo stream. A number of roentgenograms, illustrating th various types of lesions, are reproduced. The clinic and diagnostic features of the infection are outline in detail.

KEITH, Rochester, Minn.

Diseases of Blood, Heart and Blood Vessels and Spleen

THE SURGICAL TREATMENT OF MALFORMATIONS OF TH HEART IN WHICH THERE IS PULMONARY STENOS OR PULMONARY ATRESIA. ALFRED BLALOCK an HELEN TAUSSIG, J. A. M. A. **128**:189 (May 1 1945.

An operation providing for increased blood flow t the lungs of patients with congenital malformations o the heart consists in anastomosing a branch of th aorta (innominate or subclavian artery) to one of th pulmonary arteries. This procedure has been success fully carried out in 3 children, aged 1 year, 11 year and 6 years, respectively, with resultant significa relief from cyanosis and dyspnea, improved exerci tolerance and (when measured) increase in oxyge saturation of the arterial blood.

"The types of abnormalities which should be bene fited by this operation are the tetralogy of Fallo pulmonary atresia with or without dextroposition o the aorta and with or without defective developme of the right ventricle, a truncus arteriosus with bron chial arteries, and a single ventricle with a rudimentar outlet chamber in which the pulmonary artery is dimin tive in size. The operation is indicated only whe there is clinical and radiologic evidence of a decrea in the pulmonary blood flow. The operation is n indicated in cases of complete transposition of the gre vessels or in the so-called 'tetralogy of Fallot of th Eisenmenger types,' and probably not in aortic atresi It must be emphasized that the operation should not b performed when studies reveal a prominent pulmonar conus or pulsations at the hili of the lungs."

BAIRD, Wauwatosa, Wis.

ACUTE GAUCHER'S DISEASE IN AN INFANT. J. P. GARRAHAN, A. C. GAMBIRASSI, J. M. ALBORES and J. MORAN, Arch. argent. de pediat. **23**:3 (Jan.) 1945.

A historical note is given, and a clinical case occurring in a 7 month old infant is reported.

The most striking clinical features in the case were a rapid course, hepatosplenomegaly and a neurologic syndrome characterized by opisthotonos, strabismus, laryngospasm and idiocy. A familial tendency was present. Puncture of the spleen showed typical Gaucher cells, and encephalography revealed evidences of cerebral lesions.

The differential diagnosis is thoroughly discussed, and the clinical picture is summarized.

The authors stress the presence of opisthotonos from the time of birth as a sign not usually found in typical cases of acute Gaucher's disease.

The patient died outside the hospital, and autopsy was not performed.

CASSORLA, Chicago.

HEREDITARY BLOOD DYSCRASIAS IN INFANCY. MARTAGÃO GESTEIRA, J. de pediat., Rio de Janeiro **10**: 243 (June) 1944.

The author discusses the hereditary blood dyscrasias of children and gives illustrative photographs and charts. These diseases are classified as of the white cells, of the blood platelets (hemophilia, constitutional thrombopenia and thrombopenic purpura) and of the red cells (congenital hemolytic anemia, sickle cell anemia, erythroblastosis fetalis, von Jaksch's anemia and Cooley's anemia [familial erythroblastic anemia]).

SANFORD, Chicago.

THE PLESSIGRAM IN CHILDREN. MARTAGÃO GESTEIRA, Rev. brasil. med. **1**:26 (Aug.) 1944.

The author, after twenty-five years of study, puts forth the interesting hypothesis that a plexigram shows certain diameters of the heart that are associated with certain dimensions of the hand. In children with cardiopathy there is therefore an increase in the size of the heart that makes the diameters of the plexigram greatly in excess of the corresponding dimensions of the hand.

SANFORD, Chicago.

Diseases of Nose, Throat and Ear

THE ABUSE OF VASOCONSTRICTORS IN HAY FEVER AND VASOMOTOR RHINITIS. LOUIS STERNBERG, New York State J. Med. **44**:1573 (July 14) 1944.

The use of nose drops containing ephedrine, epinephrine and various related compounds is greatly abused by both physicians and the public. These substances should be used as sprays only, not in the form of drops, and applied only once or twice daily. It is best to use the sprays when symptoms are most severe.

AIKMAN, Rochester.

THE TREATMENT OF CHRONIC SUPPURATIVE OTITIS MEDIA BY THE LOCAL APPLICATION OF PENICILLIN AND OTHER DRUGS. E. G. COLLINS and K. E. A. HUGHES, J. Laryng. & Otol. **59**:81 (March) 1944.

Collins and Hughes present a series of 23 cases of chronic suppurative otitis media, in 9 of which penicillin was applied locally. The investigation involved examination of over 300 aural smears and 540 cultures, thereby permitting an interesting bacteriologic study of chronic suppurative otitis media. Rigid aseptic technic was followed in order to avoid meatal contamination, material for cultures and smears being taken by a platinum loop passed through the perforation into the middle ear. In the initial cultures, staphylococci were found three times, "coliform" bacilli ten times, Proteus vulgaris thirteen times and diphtheroids six times, a mixed growth being common. It is believed that chronic suppurative otitis media furnishes an outstanding example of antibiosis.

Nine patients were treated by local application of penicillin; 4 of these had a dry and sterile ear after treatment. A similar result was observed in 12 of the remaining 14 patients, after other therapy, as follows: local use of boric acid in 75 per cent alcohol; local use of boric acid–iodine powder; local application of sulfonamide compounds (sulfanilamide powder, succinylsulfathiazole powder, a 30 per cent solution of acetylsulfanilamide and a 15 per cent "cream suspension" of crystals of sulfathiazole [Mikraform Sulfathiazole]) and peroral administration of sulfathiazole, in a dosage of 39 Gm. in seven days. It was felt that successful treatment of chronic suppurative otitis media was hindered greatly by the presence of "coliform" bacilli, P. vulgaris and diphtheroids. In some of the cases a 30 per cent solution of acetylsulfanilamide combined with penicillin proved to be fairly successful clinically in preventing this complication.

The authors emphasize the importance of daily careful toilet of the ear carried out by the otologist himself. Such care is believed to be in no small way responsible for obtaining dry, sterile ears for 70 per cent of the patients, including both the group treated with penicillin and those treated with other drugs.

The technic of the local use of penicillin, as well as its clinical and bacteriologic effects, is well illustrated with case records, the authors concluding that the types of organisms present and the difficulties of application will limit its use. Of all the bacilli found in the aural discharge, staphylococci and P. vulgaris are the greatest enemies, and when in combination they appear to be intractable to treatment. Penicillin was not used parenterally in this study.

LEJEUNE and STEELE, New Orleans.
[ARCH. OTOLARYNG.]

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

EFFECT OF LIGATION OF PANCREATIC DUCTS ON THE SERUM PHOSPHATASE. MARTIN M. NOTHMANN, Proc. Soc. Exper. Biol. & Med. **57**:15 (Oct.) 1944.

The pancreatic ducts of 10 dogs were ligated, and the phosphatase activity of the serum was studied. No change occurred in the acid phosphatase, but a sixfold to eightfold increase in the alkaline phosphatase was found in the 7 dogs which survived. A moderate increase also was noted in the 3 animals which died within twenty-four to seventy-two hours postoperatively.

Human patients with carcinoma of the pancreas were found to have high alkaline serum phosphatase values, and 3 patients having steatorrhea with evidence of deficiency of pancreatic juice also had high values. Further work is necessary to know the diagnostic value of alkaline serum phosphatase activity in cases of pancreatic disease.

HANSEN, Galveston, Texas.

PROTEOLYSED BEEF IN THE TREATMENT OF COELIAC DISEASE. A. C. ADAMSON and DAVID LEWES, Brit. M. J. **2**:370 (Sept. 16) 1944.

The importance of a diet rich in protein is well recognized in the treatment of celiac disease. The purpose of this paper is to present a method of treating celiac disease with proteolyzed beef, which is easy to prepare, is taken readily by the patient and contains a high concentration of protein.

The method used for preparation of the material is to place 6 pounds (2,700 Gm.) of minced lean meat in a steam pan with 15 Gm. of papain and 100 ounces (3,000 cc.) of water. This mixture is heated to 60 C. and maintained at this temperature for three hours. The material is then raised to 100 C. and boiled vigorously for ten minutes. The hot digest is then strained through a cloth, cooled in a refrigerator and strained to remove the residual fat. The volume is then adjusted to contain 6 pints (3 liters) of water. One pint (500 cc.) is issued to each patient each day. The advantages of proteolyzed beef are as follows:

1. Proteolyzed beef yields in concentrated solution first-class protein in the form of easily digested and assimilable peptones, polypeptides and amino acids. 2. The digest is free from indigestible and particulate matter, such as fibrous tissue. 3. Being reduced to a small volume (20 ounces [600 cc.]), the equivalent of 1 pound (453 Gm.) of beef a day can be taken by a young child over an indefinite period, whereas use of a similar quantity of predigested beef would not be feasible. 4. Proteolyzed beef is not unpleasant to the taste and resembles broth; but what is more important is that it is taken readily, and sometimes eagerly, by young children. 5. The absence of serious technical difficulties renders the routine preparation of the digest practical in any hospital possessing a well equipped dispensary.

The authors report on 2 patients who responded well to the therapy. In the summary, the authors state that they hope that this new method of treatment, based on the principle of the need of a high protein diet for patients with celiac disease, will stimulate further clinical trials. BIRDSONG, Charlottesville, Va.

ATRESIA OF THE BILE DUCTS. M. T. VALLINO and A. MAGALHAES, Arch. argent. de pediat. **22**:304 (Oct.) 1944.

The case of a 2 month old girl who had had severe jaundice since three days after birth is reported. A diagnosis of congenital malformation of the bile ducts was made. Laparotomy showed atresia of the bile ducts, but no attempt at restoration was made and the infant died a month after the operation. The autopsy confirmed the diagnosis. CASSORLA, Chicago.

DIVERTICULITIS AND APPENDICITIS IN A TWENTY-SIX MONTH OLD GIRL. J. DAMIANOVICH, Arch. argent. de pediat. **23**:48 (Jan.) 1945.

The occurrence of diverticulitis and appendicitis in a 26 month old girl, is reported. Medical care was sought because the child presented a high temperature and presumably had been exposed to measles. No abdominal pain or gastrointestinal symptoms were present.

On physical examination cryptic tonsillitis was found, and palpitation of the abdomen revealed tenderness in the right lower quadrant. A diagnosis of appendicitis was made and surgical intervention advised. Laparotomy disclosed appendicitis and diverticulitis; histologic studies confirmed this diagnosis.

Four days after the operation Koplik spots were found, and subsequently typical measles developed. The patient made, finally, a complete recovery.

The importance of complete physical examination is stressed. CASSORLA, Chicago.

ACUTE DIARRHEA IN INFANCY AND CHILDHOOD. ARTURO J. ABALI and JUAN MARTINEZ CRUZ, Bol. Soc. cubana de pediat. **16**:386 (Oct.) 1944.

In Cuba, specific enteric infection is the most frequent cause of diarrhea among well nourished infants. Of 116 patients 53.4 per cent had stools from which Shigella and Salmonella organisms were cultured. In the epidemiology of such diarrheas, contact with infected persons and carriers as well as transmission by flies are the important factors. These organisms may give rise to atypical clinical pictures which offer serious diagnostic difficulties. Sulfaguanidine, succinyl sulfathiazole, sulfathiazole and sulfadiazine have been effective in therapy. The authors feel that the diet for persons with enteric infection should be low in protein and fat, but for persons in whom enteric infection is secondary to parenteral infection the diet should be high in protein and low in fat and starch. Ample amounts of B complex vitamins are advised. The authors close with a critical review of prevalent ideas on the causes of diarrhea. KEITH, Rochester, Minn.

Nervous Diseases

CEREBROVASCULAR ACCIDENTS FOLLOWING EPINEPHRINE INJECTIONS. L. L. APPLEBAUM, J. Allergy **15**:39 (Nov.) 1944.

The occurrence of a cerebrovascular accident in young men following the injection of 0.5 cc. of a 1:1,000 solution of epinephrine hydrochloride is reported. The patients had bronchial asthma and, as far as known, had not had epinephrine before. The left-sided palsy was transient in 1 case. In the other the palsy on the right side lasted for several months.

An awareness of the possibility of such accidents and exercise of caution in the administration of epinephrine hydrochloride are recommended. HOYER, Cincinnati.

RECOVERY IN A CASE OF STAPHYLOCOCCAL MENINGITIS TREATED BY CHEMOTHERAPY. DAVID BRASH, Glasgow M. J. **24**:107 (Oct.) 1944.

The patient was treated with sulfathiazole and sulfadiazine and recovered. The drugs were used intravenously and orally. SNELLING, Toronto, Canada.

TRAUMATIC SUBDURAL EFFUSION IN CHILDREN. JOHN P. LANIGAN, Lancet **2**:686 (Nov. 25) 1944.

Within six months, 3 children in the Richmond Hospital, Dublin, had subdural hydroma or effusion after a head injury which was not associated with any initial concussion or amnesia and therefore gave no cause for immediate anxiety.

In the cases recorded, the condition appears to have been an extravasation of cerebrospinal fluid through a tear in the arachnoid membrane—though such a tear was never actually seen. All these conditions may be regarded as examples of pure extracerebral lesions. The lack of progression and persistence of symptoms are emphasized by comparison with a case of extradural

emorrhage. It is suggested that in such cases the est treatment is early operation.

LANGMANN, New York.

Psychology and Psychiatry

PSYCHOMOTILITY IN BEHAVIOR DISORDERS AS SEEN IN THE HANDWRITING OF CHILDREN. SELNA SCHRYVER, J. Nerv. & Ment. Dis. **100**:64 (July) 1944.

The study of a subject's handwriting gives a clue to is psychomotility, and through this, information as to is personality makeup can be obtained. With children he study of handwriting is handicapped by the subject's ifficulty in spelling and by lack of routine. To over- ome this the author has worked out a test in which hildren are asked to write a number of simple basic arts of the usual letters at least twenty times each. In series of 100 specimens of handwriting written by a roup of children with various psychiatric disorders here were indications of the intelligence level, character raits and emotional maturity of the writer. Aggressive, oisy children produced samples marked by great pres- ure and angularity, whereas preoccupied children with eelings of inferiority had small letters characterized by hort endings, low pressure and hesitating beginnings. Psychotic children showed splitting of forms, exaggera- ion of size and contraction and alteration of forms. n evaluation of the samples, the gestalt, as well as etails, must be considered for a rounded picture.

CHODOFF, Langley Field, Va.
[ARCH. NEUROL. & PSYCHIAT.]

LATE BEHAVIORAL ASPECTS FOUND IN CASES OF PRENATAL, NATAL AND POSTNATAL ANOXIA. MARY I. PRESTON, J. Pediat. **26**:353 (April) 1945.

In 2 cases of birth anoxia involving the second born f identical twins the infants were intelligent but ex- ibited abnormal behavior. One patient showed apathy ith a greater degree of anoxia and the other hyper- ctivity with a lesser degree of anoxia. These cases ed to collection from the author's practice of 132 cases f prenatal, natal or postnatal anoxia. Ninety-seven of he patients were intelligent. Hyperactivity appeared n 36 and apathy in 33; the anoxia had also produced pilepsy in 28 patients and, by destruction of cortical ells, had left 35 others subnormal in intelligence, as well as hyperactive, apathetic or epileptic. Incoordina- ion occurred throughout the series.

The neonatal period was normal with respect to olor, time of crying and breathing for 8 infants in whom the anoxia occurred in the prenatal period, giving ime for recovery of the fetal respiratory center before irth. The subsequent behavior of these infants, how- ver, showed damage to the brain, as in the rest of the eries. The result was either apathy or hyperactivity n movements, sleep and crying, and the unit of brain ells governing appetite was rendered nonfunctional for many years.

In the postnatal period anoxia resulting from per- ussis and pneumonia brought about the same damage in 5 patients; physical inferiority began to be evident in ll, but the intelligent children began teething, standing, itting up and walking at the usual time, indicating that here was no damage to the guiding neurons which were undeveloped at the time of the anoxia.

In the run-about period the increase of environmental timulation made the abnormal behavior still more in- ense: The hyperactive patients became more uncon- rollable in their hyperexcitability and the apathetic more confused and inadequate to the increased demands of life, so that they, too, were more unmanageable. As a result, all the parents complained that the children did not seem to take in what was said; discipline had no effect, and they did not learn from experience. Their social contacts were disturbing, their speech was defective, and their reactions remained at the instinctive-emotional level for years.

The school age was tragic, with use of mentality nullified by the anoxic effects, the victims being unable to participate like other pupils in the learning process or in school life. Besides the warping, there was also an arrest of personality development, seemingly because maturational mechanisms had been interfered with, and infantile rages with massive movements, excessive destructiveness, overwhelming jealousy and cruelty continued for years. The presence of these patients was a burden and a disrupting influence in the home and a source of irritation in social life (68 per cent were not liked by any one, and 64 per cent were unable to like any one), and all were a sore trial at school. The parents turned against 49 per cent of the children.

Treatment was greatly facilitated when parents and teachers understood that the behavior of these children was due to their having been made cripples by the anoxia. Steps were taken to increase their nervous and emotional stability. By this means the intelligence quotients of the 6 who were retested increased 16, 19, 19, 23, 27 and 28 points, respectively. Recovery of the untreated patients took place in varying degrees in from five to twelve years. AUTHOR'S ABSTRACT.

THE RELATIONSHIP BETWEEN FREQUENCY AND DURATION OF MOMENTS OF STUTTERING. WENDELL JOHNSON and WILLIAM H. COLLEY, J. Speech Disorders **10**:35 (March) 1945.

Twenty stutterers, 19 males and 1 female, whose ages ranged from 14 years and 6 months to 33 years and 6 months, with an average of 21 years and 1 month, read a 1,000 word, phonetically edited passage under carefully controlled conditions. As the subjects read, the duration of each stuttered moment was recorded on a tape by electromagnetic pens attached to noiseless signal keys manned by two observers, working independently. On the basis of a low but positive correlation between frequency and duration of moments of stuttering it is concluded that both frequency and duration of moments of stuttering are measures of severity or amount of stuttering but that neither is to be regarded as a complete measure, since the two do not consistently show a high correlation. Frequency alone or duration alone cannot be employed as a measure of the amount or the severity of stuttering. The severity of stuttering immediately after any one moment of stuttering cannot be predicted from the duration or the severity of the preceding moment of stuttering. The authors caution that any conclusions must be evaluated with regard to the fact that the stuttering was measured in a reading situation only.

PALMER, Wichita, Kan.

Diseases of the Eye

EFFECT OF RETINAL EXTRACTS ON GROWTH OF BLINDED MALE RATS. LUDVIG G. BROWMAN and AUDRA A. BROWMAN, Proc. Soc. Exper. Biol. & Med. **57**:171 (Nov.) 1944.

Extracts of the retinas of freshly butchered cattle were prepared by grinding with sand, leached over-

night and filtered. This material was injected into male rats which had had bilateral ocular enucleation. Injections into the rats began when they were 15 days of age and were continued for ten weeks; when the rats were 100 days old, they were killed, and autopsies were performed. The weights of the animals and the weights of the thyroid, seminal vesicles and testes approached those of 20 male rats with normal eyes, whereas the weights of the animals which had been subjected to bilateral ocular enucleation were definitely lower. Spermatozoa were found to be present in the testes of normal animals at the age of 35 to 40 days and in the testes of rats which had had bilateral ocular enucleation at the age of 50 days, but in the animals subjected to bilateral ocular enucleation which were given injections of bovine retina spermatozoa they were present at 45 days of age. The authors state that retinal extracts of bovine eyes apparently have an alleviating effect on the retardation of weight and the delayed sexual maturity characteristic of male rats which have had bilateral ocular enucleation.

HANSEN, Galveston, Texas.

Teeth and Dentistry

STUDIES ON THE INCIDENCE AND CAUSE OF DENTAL DEFECT IN CHILDREN: IV. MALOCCLUSION. MARCU BRUCKER, J. Dent. Research **22**:315, 1943.

The subjects of this study were 1,668 white school children (863 boys and 805 girls), aged 5 to 15 years, in Newark, N. J. The average numbers of dental cavities per child were found to be as follows: with true malocclusion, 4.3 boys and 4.3 girls; with malocclusion of the transitional dentition, 4.1 boys and 4.2 girls; with no malocclusion, 2.4 boys and 2.9 girls. The non-Jewish children with malocclusion showed a definitely higher incidence of caries than did Jewish boys or girls with this condition, whether of the deciduous, the permanent or the transitional dentition.

SANFORD, Chicago. [ANGLE ORTHODONTIST]

THE SIGNIFICANCE OF DELAYED OSSIFICATION IN THE TREATMENT OF CONGENITAL CLUBFOOT. DONALD W. LEONARD, J. Pediat. **26**:379 (April) 1945.

The present treatment of congenital clubfoot, whatever mechanical appliance or clinical procedure is chosen, accomplishes only the correction of the deformity; time is needed for the biologic process of ossification to take place after this reduction has been completed. Bone formation progresses at a rate peculiar to the individual; but the centers of ossification have usually appeared by the end of the third year, so that the first three years of life must be considered the most critical period for successful treatment. The variations in the individual time schedule of ossification of the tarsal bones are therefore of primary importance.

In order to make it possible to measure quickly the degree of ossification present in a case, an ossification index for the foot is proposed. This index is constructed from a set of figures arbitrarily chosen to represent the latest possible normal age at which the centers may appear, judging from tabulations by twelve different authors. The figures are as follows:

Calcaneus	Present at birth	B
Talus (astragalus)	Present at birth	B
Cuboid	Present at birth	B
Tibia (distal epiphysis)	Appears before age of 1 year	1
Lateral (III) cuneiform bone	Appears before age of 1 year	1
Fibula (distal epiphysis)	Appears before age of 2 years	2
Medial (I) cuneiform bone	Appears before age of 3 years	3
Central (II) cuneiform bone.	Appears before age of 4 years	4
Navicular	Appears before age of 4 years	4

The normal ossification index (age 4) is 4-BBB-112344.

To use the ossification index, the actual age of the patient is posted; it is followed in chronologic order according to the tabulation just given, by figures representing the ossification centers which are present; zeros are substituted for the centers which have not appeared. The normal index for a given age is the combination which lists all of the figures for ages up to and including the actual age. With use of this index it is possible quickly to detect delayed ossification by inspecting any roentgenogram of a foot. The figures have been chosen to represent the extreme upper limit of normal development; hence absence of any one of them in the index for that age is so definitely pathologic that sex differences and normal variations may be disregarded.

The results of a preliminary study by this method of 24 patients with clubfoot is presented in this paper. The index for each of several sets of roentgenogram negatives taken during the course of the regular treatment has been evaluated. From this tabulation it is apparent that delayed ossification occurred in most of the patients who eventually required radical operation on the bone and that normal ossification was present in all of the patients who required only simple manipulation and temporary fixation. Because of these observations, it seems legitimate to recommend that surgeons consider the time schedule of ossification in their routine treatment of clubfoot. Abnormalities in this respect apparently have a good deal to do with the prognosis and may justify change in the plan of treatment.

Inasmuch as similar delay in the appearance of ossification centers occurs with hypothyroidism, the use of thyroid is suggested as a medical adjunct to the usual surgical treatment. This medical treatment may therefore be indicated for any patient with clubfoot whose ossification index has shown delay. If the rate of bone formation in such a patient is not accelerated by this means, the orthodox treatment may be expected to fail, and a decision to perform one of the radical surgical procedures may be made earlier and the total period of disability shortened. AUTHOR'S ABSTRACT.

Miscellaneous

THE ECONOMY OF WAR AND THE EDUCATION OF THE VENEZUELAN PEOPLE. LUIS B. PRIETO F., Bol. Inst. internac. am. protec. a la infancia **18**:102 (March) 1944.

The economy of war, the aim of which is to defend the nation, should not neglect the education of the people. The preparation for war and the creation of an ideal should also be considered as necessary elements of defense, since an illiterate country, as a result of the limited capacity of the population to understand the problems and to resist the aggression, is easily overcome.

In order to assign to education the necessary resources, it is essential to eliminate useless expenditures in public administration. The Venezuelan teachers gathered in the F. V. M. (Venezuelan Teachers' Federation) once more express themselves in favor of the elaboration of a scientific educational budget. The resources of the Venezuelan educational budget should contribute decisively to fulfilment of the educational needs of the population. To attain such a purpose, it is essential that the funds be employed to assist in meeting the most urgent needs and that, as much as possible, the attention of the government be not monopolized by less important activities, to the detriment of problems demanding efficacious and immediate solution. EDITOR'S SUMMARY.

Book Reviews

The Chemistry and Pharmacy of Vegetable Drugs: Dealing with the Derivation and Properties of All the Principal Vegetable Drugs; for Practitioners and Students. By Noel L. Allport, F.I.C., Research Chemist, The British Drug Houses, Ltd. Cloth. Price, $4.75. Pp. 258, with 17 tables and 126 figures. Brooklyn: Chemical Publilshing Company, Inc., 1944.

This book contains twenty-two chapters classifying the drugs, some of which are official (in the Pharmacopeia of the United States and the National Formulary) and some nonofficial, as to their active principles, that is, as alkaloids, glucosides, etc.; therapeutic action, that is, as diuretics, laxatives, expectorants, etc., and as to their use in pharmaceutic practices and preparations into which they enter

Much space is given to alkaloidal drugs, eight chapters being devoted to this type of drug with tables showing the drug, part used, active principles, percentage of active principle, physiologic action and therapeutic uses.

The book also has several similar tables of other drugs, many of which are less important than that dealing with the alkaloids.

The figures, one hundred and twenty-six in number, are reproductions from photographs of plants, crude drugs and various types of equipment.

The book contains over one hundred monographs on the vegetable drugs, showing their origin and methods of collection and preparation, the constituents, the chemistry and pharmacology, their actions and in most cases their chemical names and structural formula.

Also, for many drugs, the technic and methods of collections, preparation and assay are given.

Microbial Antagonisms and Antibiotic Substances. By Selman A. Waksman, Ph.D., Sc.D. Price, $3.75. Pp. 350, with 34 figures and 48 tables. New York: The Community Fund, 1945.

This volume of 350 pages is a timely contribution to the subject of antibiotic substances, produced by microorganisms—bacteria, fungi, etc.—penicillin, tyrothrycin streptomycin and others. The author surveys the field and calls attention to the natural habits of microorganisms: how they are held at bay by natural substances produced by other forms of life; how they get along with each other under varying circumstances, sometimes in symbiotic relation and at other times as direct parasites; the reactions which tend to bring about the latter condition; how these antagonist reactions are affected when many types of organisms are present, and what effect they have on disease-producing conditions in man. He considers organisms in themselves—bacteria as well as fungi—their nature, their habitat and their method of bringing about their antagonistic action to micro-organisms and related subjects. It is an interesting volume, one that is complete and up-to-date and written by some one who has done authentic work in this field of endeavor. It contains a table of antibiotic substances on which some late work has been done and a general index to some pertinent articles.

This is a good reference book for any one who wishes to understand the character and mechanisms of molds.

O Misterio do Noma (Três Casos em Marilia). By J. Coriolano de Carvalho. Price, not given. Pp. 44, with 8 illustrations. Rio de Janeiro: Jornal do Commercio, Rodrigues & Co., 1944.

The author reviews what is contained in the literature about the etiology, pathology, diagnosis and treatment of noma, showing the mysteries which still remain unexplained in this disease. His personal contribution is the clinical report of the cases of 3 children, 2, 4 and 5 years of age, whom he followed and treated in Marilia, São Paulo, Brazil. After commenting on the different precipitating factors, such as individual tendency, cleanliness and nutrition, the author states the following conclusions:

1. Noma preferably attacks children already undermined by other diseases, such as measles and scarlet fever. 2. It is a highly lethal condition, and when the patient survives a severe scar remains, which requires plastic surgical treatment. 3. It is a disease of the poor people. 4. Contrary to the usual belief that it is a disease of the past, it still occurs at the present time in Rio de Janeiro, Minas Geraes and São Paulo. 5. The only therapeutic measures which still seem to be effective are blockage of the sympathetic nervous system, application of the electric scalpel and use of antigangrene serum and vitamins of the B constellation. 6. Spontaneous cure has occurred, but total spontaneous restoration of the tissues has never been observed. 7. The author thinks that noma results from deficiency of vitamins, mainly of the B constellation.

It would probably have been wiser for the author to remain faithful to the title of his paper instead of making the last statement without any experimental evidence to support it.

News and Comment

GENERAL NEWS

Dr. Kaiser Honored.—Dr. Albert D. Kaiser, professor of child hygiene at the University of Rochester School of Medicine and Dentistry, Rochester, N. Y., was recently awarded the Rochester Civic Medal by the Rochester Museum Association. Dr. Kaiser has also been elected for a three year term to the board of trustees of the Rochester Academy of Medicine.

Intermountain Pediatric Lectureship.—Dr. Joseph Stokes Jr., professor of pediatrics in the University of Pennsylvania School of Medicine, gave the first lectures of the Intermountain Pediatric Lectureship of the University of Utah School of Medicine, on July 16 and 17, on "Studies of Infectious Hepatitis" and "The Use of Gamma Globulin in Infectious Hepatitis and Other Communicable Diseases." Dr. Ashley Weech, professor of pediatrics and head of the Children's Research Foundation of the University of Cincinnati, presented two lectures, on July 26 and 27, on "The Physiologic Consequences of Inadequate Dietary Protein" and "The Role of Cortical Development in the Behavior of the Infant."

Directory of Pediatric Societies *

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary-General: Dr. L. Emmett Holt Jr., 477 First Ave, New York 16.
Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. H. P. Wright, 1509 Sherbrooke St. W., Montreal.
Place: New York. Time: Postponed indefinitely.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

Associação Paulista de Medicina, Secção de Pediatrias

President: Dr. Vicente Lara.
First Secretary: Dr. Armando de Arruda Sampaio.
Second Secretary: Dr. Luiz Augusto Monteiro Toledo, Av. Brigadeiro Luiz Antonio 393, 1° Andar, São Paulo, Brazil.
Time: Twelfth of every month, 8:30 p. m.

British Paediatric Association

President: Prof. L. G. Parsons, 58 Calthorpe Rd., Five Ways, Birmingham.
Secretary: Dr. Donald Paterson, 27 Devonshire Pl., London, W. 1.

Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. E. Gjørup, Dronning Louises Børnehospital, Copenhagen.

Nederlandische Vereeniging voor Kindergeneeskunde

President: Dr. J. H. G. Carstens, Servaasbolwerk 14ª, Utrecht.
Secretary: Dr. R. P. van de Kasteele, Laan van Poot 340, 's Gravenhage.
Place: Different places. Time: Three times a year.

Paediatrický Spolok na Slovensku

President: Dr. A. J. C. Chura, Lazaretská 11, Bratislava.
Secretary: Dr. P. Rados, Lazaretská 6, Bratislava.
Place: Pediatric Clinic, University Bratislava. Time: Six times a year.

Royal Society of Medicine, Section for the Study of Disease in Children

President: Prof. Norman Capon, 49A Rodney St., Liverpool, England.
Secretary: Dr. J. N. O'Reilly, 46 Harley St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

Palestine Jewish Medical Association, Section of Physicians of Children's Diseases

President: Prof. S. Rosenbaum, 26 Bialkstr., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

Sociedad Cubana de Pediatria

President: Dr. Teodosio Valledor y Campos, Habana.
Secretary: Dr. Carlos Hernandez Miyares, Hospital Nuestra Señora de las Mercedes L y 21, Apartado, 2430, Habana.
Place: Cátedra de Clinica Infantil, Hospital Nuestra Señora de las Mercedes y Hospital Municipal de Infancia, Habana. Time: Last Wednesday of every month.

Sociedad Ecuatoriana de Pediatria

President: Dr. Francisco de Icaza Bustamente.
Secretary: Dr. M. I. Gómez Lince, P. O. Box 693, Guayaquil.

Sociedad Mexicana de Pediatria

President: Dr. Fernando López Clares, 12/a. Medellín 191, Mexico.
Secretary: Dr. Jesus Gómez Pagola, Versalles 64, Mexico.

Sociedad de Pediatría de Santiago de Cuba

President: Dr. Antonio Béguez César, Sagarra 107, Santiago de Cuba.
Secretary: Dra. Susana Texidó Vaillant, Padre Pico 57, Santiago de Cuba.
Place: Colegio Médico.

Sociedad Venezolana de Puericultura y Pediatria

President: Dr. Pedro J. Alvarez.
Secretary: Dr. Ernesto R. Figueroa, 3a Avenida 10, Bella Vista, Caracas.
Place: Hospital Municipal de Niños Jose Manuel de los Rios, Caracas.

Société de Pédiatrie de Paris

President: Dr. Leveuf, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Maladies, 149 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

Uruguayan Society of Pediatrics

President: Dr. José Alberto Praderi, Eduardo Acevedo 1132, Montevideo.

Secretary: Dr. Héctor Fossatti, Durazno 1882, Montevideo.

NATIONAL

American Medical Association, Scientific Assembly, Section on Pediatrics

Chairman: Dr. John Aikman, 184 Alexander St., Rochester, N. Y.

Secretary: Dr. Gilbert J. Levy, 188 S. Bellevue Blvd., Memphis, Tenn.

In compliance with the request of the Office of Defense Transportation and in the interest of the national war effort a meeting will not be held in 1945.

American Academy of Pediatrics

President: Dr. Joseph S. Wall, 1864 Wyoming Ave. N. W., Washington, D. C.

Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.

American Hospital Association, Children's Hospital Section

Chairman: Dr. Joelle C. Hiebert, 299 Main St., Lewiston, Maine.

Secretary: Dr. W. Franklin Wood, McLean Hospital, Waverly, Mass.

American Pediatric Society

President: Dr. C. Anderson Aldrich, Mayo Clinic, Rochester, Minn.

Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid Ave., St. Louis 8.

Canadian Society for the Study of Diseases of Children

President: Dr. H. S. Little, 300 Dufferin Ave., London, Ontario.

Secretary-Treasurer: Dr. Elizabeth Chant Robertson, 67 College St., Toronto 2.

Society for Pediatric Research

President: Dr. Edward M. Bridge, 219 Bryant St., Buffalo, N. Y.

Secretary: Dr. Mitchell I. Rubin, 1740 Bainbridge St., Philadelphia 46.

SECTIONAL

Intermountain Pediatric Society

President: Dr. Robert Alway, University of Utah School of Medicine, Salt Lake City 2.

Secretary-Treasurer: Dr. L. Paul Rasmussen, 1020 Boston Bldg., Salt Lake City 1.

Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

New England Pediatric Society

President: Dr. William P. Buffum, 122 Waterman St., Providence, R. I.

Secretary-Treasurer: Dr. James Marvin Baty, 1101 Beacon St., Brookline, Mass.

Place: Boston Medical Library. Time: Three meetings a year, occurring from September to May.

North Pacific Pediatric Society

President: Dr. M. L. Bridgeman, 1020 S. W. Taylor St., Portland, Ore.

Secretary: Dr. C. G. Ashley, 833 S. W. 11th Ave., Portland, Ore.

Northwestern Pediatric Society

President: Dr. George B. Logan, 102 Second Ave. S. W., Rochester, Minn.

Secretary-Treasurer: Dr. Northrop Beach, 1009 Nicollet Ave., Minneapolis.

Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

Rocky Mountain Pediatric Society

President: Dr. G. R. Fisher, 23 E. Pikes Peak Ave., Colorado Springs, Colo.

Secretary: Dr. Joseph H. Lyday, 1850 Gilpin St., Denver.

Southern Medical Association, Section of Pediatrics

Chairman: Dr. William Weston Jr., 1428 Lady St., Columbia, S. C.

Secretary: Dr. Angus McBryde, 604 W. Chapel Hill St., Durham, N. C.

STATE

Alabama Pediatric Society

President: Dr. Jerome C. Chapman, 2160 Highland Ave., Birmingham.

Secretary-Treasurer: Dr. Ruth Berrey, 2021–6th Ave. N., Birmingham.

Arizona Pediatric Society

President: Dr. Vivian Tappan, San Clemente, Tucson.

Secretary: Dr. Hilda Kroeger, Arizona State Health Dept. (Maternal and Child Welfare Division), Phoenix.

Arkansas State Pediatric Association

Chairman: Dr. C. B. Billinsgsley, 1425 N. 11th St., Fort Smith.

Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

California State Medical Society, Section on Pediatrics

Chairman: Dr. Charles W. Leach, 2000 Van Ness Ave., San Francisco 9.

Secretary: Dr. Chester I. Mead, 1930 Truxton Ave., Bakersfield.

Florida State Pediatric Society

President: Dr. Ludo Von Meysenbug, Box 3356, Daytona Beach.

Secretary: Dr. Robert Blessing, 409 Blount Bldg., Ft. Lauderdale.

Place: Concurrent with state association meeting at time of convention.

Georgia Pediatric Society

President: Dr. Ruskin King, 10 W. Taylor St., Savannah.

Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. Edward T. Wakeman, 129 Whitney Ave., New Haven.

Secretary: Dr. Herman Yannet, Southbury Training School, Southbury.

Time: Three meetings a year.

Illinois State Medical Society, Section on Pediatrics

Chairman: Dr. Craig D. Butler, 715 Lake St., Oak Park.
Secretary: Dr. A. J. Fletcher, 139 N. Vermilion, Danville.

Indiana State Pediatric Society

President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Mathew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

Iowa Pediatric Society

President: Dr. Mark L. Floyd, Children's Hospital, Iowa City.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bldg., Davenport.

Medical Society of State of New York, Section on Pediatrics

Chairman: Dr. Carl H. Laws, 12 Pierrepont St., Brooklyn, N. Y.
Secretary: Dr. George R. Murphy, 292 Madison Ave., New York.
Place: Same as State Society. Time: Same as State Society.

Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. Elwood W. Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Secretary: Dr. P. F. Lucchesi, Philadelphia Hospital, Philadelphia.

Michigan State Medical Society, Pediatric Section

Chairman: Dr. Donald J. Barnes, 3001 W. Grand Blvd., Detroit, Mich.
Secretary: Dr. Mark F. Osterlin, Central Michigan Children's Clinic, Traverse City.
Place: Detroit. Time: September 1945.

Mississippi State Pediatric Society

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

Nebraska Pediatric Society

President: Dr. John L. Gedgoud, University of Nebraska Hospital, Omaha.
Secretary-Treasurer: Dr. Gerald C. O'Neil, 640 City National Bank Bldg., Omaha.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

New Hampshire Pediatric Society

President: Dr. MacLean J. Gill, 14 N. State St., Concord.
Secretary-Treasurer: Dr. Ursula G. Sanders, 46 Pleasant St., Concord.
Time: Twice yearly.

North Carolina Pediatric Society

President: Dr. Arthur H. London Jr., 1105 W. Main St., Durham.
Secretary: Dr. Jay M. Arena, Duke Hospital, Durham.

Northern California Pediatric Society

President: Dr. John Mott Rector.
Secretary: Dr. George Bates, 490 Post St., San Francisco.
Place: San Francisco. Time: Second Thursday of February, April, September and November.

Oklahoma State Pediatric Society

President: Dr. G. R. Russell, 604 S. Cincinnati Ave., Tulsa.
Secretary: Dr. Luverne Hays, 108 W. 6th St., Tulsa.
Place: With Oklahoma State Medical Association. Time: Annual Meeting.

South Carolina Pediatric Society

President: Dr. Lonita Boggs, 301 E. Coffee St., Greenville.
Secretary-Treasurer: Dr. Hilla Sheriff, 429 Wade Hampton Office Bldg., Columbia 10.

Texas Pediatric Society

President: Dr. F. H. Lancaster, 4409 Fannin St., Houston.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmount Ave., Dallas.

Virginia Pediatric Society

President: Dr. L. E. Sutton Jr., Medical College Hospital, Richmond.
Secretary: Dr. Emily Gardner, 1100 W. Franklin St., Richmond 20.

West Virginia State Medical Society, Section on Pediatrics

President: Dr. Andrew Amick, 1021 Quarrier St., Charleston.
Secretary: Dr. A. A. Shawkey, Professional Bldg., Charleston.

LOCAL

Academy of Medicine of Cleveland Pediatric Section

Chairman: Dr. Charles L. Ruggles, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. Walter Heymann, 2103 Adelbert Rd., Cleveland.
Place: Cleveland Medical Library Bldg. Time: 8:15 p. m., October, December, February and April.

Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. John M. Ross, 530 St. Claire Ave. W., Toronto, Canada.
Secretary: Dr. J. H. Ebbs, 13 Queen's Park, Toronto, Canada.
Place: Academy of Medicine. Time: Third Thursday of each month.

Bronx Pediatric Society

President: Dr. Jacob H. Turner, 121 W. 197th St., New York.
Secretary: Dr. Harry S. Pizer, 1726 Davidson Ave., New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. Kenneth G. Jennings, 159 Midwood St., Brooklyn.
Secretary: Dr. Joseph Battaglia, 713 Bushwick Ave., Brooklyn 21.
Place: Granada Hotel. Time: 8:45 p. m., fourth Wednesday of each month except May, June, July, August and September.

Buffalo Pediatric Society

President: Dr. A. Wilmot Jacobsen, 187 Bryant St., Buffalo, N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo 9, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

Central New York Pediatric Club

President: Dr. Arthur W. Benson, 2 St. Pauls St., Troy.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Places: Various cities in New York. Time: Third Tuesday of April and October.

Chicago Pediatric Society

President: Dr. Louis W. Sauer, 636 Church St., Evanston, Ill.
Secretary: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago 12.
Place: Children's Memorial Hospital, 707 Fullerton Ave. Time: Third Tuesday of each month.

Cincinnati Pediatric Society

President: Dr. Theodore K. Selkirk, 3605 Edwards Rd., Cincinnati.
Secretary: Dr. John H. Hunt, Kemper Lane Bldg., Cincinnati.
Place: Children's Hospital, Eiland Ave., Cincinnati. Time: On call.

Dallas Pediatric Society

President: Dr. Robert A. Knox, 3701 Fairmount Ave., Dallas 4, Texas.
Secretary-Treasurer: Dr. Gladys J. Fashena, 4585 Belfort Pl., Dallas 4, Texas.
Place: Children's Medical Center: Time: 1 p. m., second and fourth Saturdays of each month.

Detroit Pediatric Society

President: Dr. Philip J. Howard, 2977 W. Grand Blvd., Detroit, Mich.
Secretary: Dr. John C. Montgomery, 564 Fisher Bldg., Detroit 2, Mich.
Place: Wayne County Medical Society. Time: 8:30 p. m., second Wednesday of each month, four meetings a year.

Fulton County Medical Society, Pediatrics Section (Atlanta, Ga.)

Chairman: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Secretary: Dr. Harry Lange, 478 Peachtree St. N. E., Atlanta.
Place: Academy of Medicine, 38 Prescott St. N. E. Time: Second Thursday of each month from October to April, 8 p. m.

Houston Pediatric Society

President: Dr. Raymond Cohen, 2300 Caroline St., Houston, Texas.
Secretary: Dr. Betty Moody, 526 Richmond Rd., Houston, Texas.
Place: College Inn, Houston. Time: Fourth Monday of each month.

Kansas City (Missouri) Pediatric Society

President: Dr. Edwin H. Schorer, 1103 Grand Ave., Kansas City.
Secretary: Dr. H. E. Petersen, Kirkpatrick Bldg., St. Joseph, Mo.
Place: Kansas City General Hospital. Time: On call.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Milo B. Brooks, 1033 Gayley Ave. W., Los Angeles.
Secretary-Treasurer: Dr. Elena Boder, 1830½ Lucille Ave., Los Angeles 26.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Abraham M. Litvak, 1145 Eastern Parkway, Brooklyn.
Secretary: Dr. Harold Levy, 750 St. Marks Ave., Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month, October to April, inclusive.

Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. Meyeron Coe, 217-02-91st Ave., Queens Village, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144-38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. Harry A. Spigel, 2647 Connecticut Ave., Washington, D. C.
Secretary-Treasurer: Dr. Perry W. Gard, 2520 Woodley Rd., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., fourth Thursday of every month.

Memphis Pediatric Society

President: Dr. W. L. Rucks, 1074 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Harry J. Jacobson, 1193 Madison Ave., Memphis, Tenn.

Milwaukee Pediatric Society

President: Dr. M. G. Peterman, 411 E. Mason St., Milwaukee 2.
Secretary-Treasurer: Dr. B. J. Malnekoff, 3213 N. Marietta Ave., Milwaukee 11.
Place: Milwaukee Children's Hospital. Time: Second Wednesday in February, April, June, October and December.

New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Alfred E. Fischer, 73 E. 90th St., New York.
Secretary: Dr. Robert O. Du Bois, 122 E. 76th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

Northern California Pediatric Society

President: Dr. John Mott Rector, 2000 Van Ness Ave., San Francisco.
Secretary: Dr. George Bates, 490 Post St., San Francisco 2.
Place: San Francisco. Time: Second Thursday of February, April, September and November.

Oklahoma City Pediatric Society

President: Dr. William M. Taylor, 625½ N. W. 10th St., Oklahoma City.
Secretary: Dr. Jeanne Shotstall, 625½ N. W. 10th St., Oklahoma City.
Place: Oklahoma Club. Time: Third Thursday of each month.

Philadelphia Pediatric Society

President: Dr. Ruth Hartley Weaver, 1719 Rittenhouse St., Philadelphia.
Secretary: Dr. Sherman Little, 1740 Bainbridge St., Philadelphia 46.
Place: College of Physicians, 19 S. 22d St. Time: 8:30 p. m., second Tuesday in October, December, February and May.

Pittsburgh Pediatric Society

President: Dr. Elwood Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Secretary-Treasurer: Dr. C. J. Stoecklein, Medical Arts Bldg., Pittsburgh 13.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate months from October to June, inclusive.

Richmond Pediatric Society

President: Dr. T. Stanley Meade, 913 Floyd Ave., Richmond, Va.
Secretary-Treasurer: Dr. Edwin L. Kendig Jr., 828 W. Franklin St., Richmond 20, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: 8 p. m., third Thursday of each month, except June, July and August.

Rochester Pediatric Society

President: Dr. William L. Bradford, 260 Crittenden Blvd., Rochester 7, N. Y.
Secretary-Treasurer: Dr. Donald D. Posson, 222 Chili Ave., Rochester 11, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee. Time: Third Friday of each month from October to May.

St. Louis Pediatric Society

President: Dr. Peter G. Danis, 634 N. Grand Ave., St. Louis 3.
Secretary-Treasurer: Dr. H. Ewing Wachter, 3720 Washington Ave., St. Louis 8.
Place: Branscome Hotel. Time: 7:00 p. m., third Thursday of each month from November to June.

Seattle Pediatric Society

President: Dr. Frederick B. Joy, Stimson Bldg., Seattle.
Secretary: Dr. Sherod M. Billington, Medical Dental Bldg., Seattle.
Place: College Club. Time: Third Friday of each month from September to June at 6:30 p. m.

Southwestern Pediatric Society

President: Dr. William Belford, 420 Walnut St., San Diego, Calif.
Secretary: Dr. Robert J. Dostal, 710 Wilshire Blvd., Santa Monica, Calif.
Place: University Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Park Bradshaw, Muskegon, Mich.
Secretary: Dr. Harry A. Towsley, University of Michigan, Department of Pediatrics and Communicable Diseases, Ann Arbor, Mich.

Westchester County Medical Society, Pediatrics Section (New York)

President: Dr. John B. Ahouse, 27 Ludlow St., Yonkers, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Place: Hospitals of Westchester County. Time: Third Thursday in November, January, March and May.